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## TABLE OF CONTENTS


**The Blood Groups in Relation to Peptic Ulceration and Carcinoma of Colon, Rectum, Breast, and Bronchus** IAN AIRD, CH.M., F.R.C.S., H. H. BENTALL, M.B., F.R.C.S., J. A. MEHIGAN, M.B., and J. A. FRASER ROBERTS, M.D., D.SC., F.R.C.P. ....315

**ABO Blood Groups and Toxaemia of Pregnancy** L. A. PIKE, M.B., and A. M. DICKINS, M.D., M.R.C.O.G. ....321

**Blood Groups in Carcinoma of the Lung** R. B. MCCONNELL, M.B., M.R.C.P., C. A. CLARKE, M.D., F.R.C.P., and F. DOWNTON, B.SC., A.R.C.S., D.I.C. ....323

**Kinking, Rotation, and Twisting of the Stomach** E. A. SPRIGGS, D.M., M.R.C.P., and O. A. MARXER ....325

**Diagnosis and Results of Treatment of Cancer of the Pancreas and Ampulla of Vater** CHARLES ROB, M.CHIR., F.R.C.S., and RODNEY SMITH, M.S., F.R.C.S. ....330

**Ischaemic Lateral Popliteal Nerve Palsy** FERGUS R. FERGUSON, M.D., F.R.C.P., D.P.H., and L. A. LIVERSEDGE, M.D., M.R.C.P. ....333

**Rouleaux Formation Intensity of Plasma and E.S.R.** S. LEWI, M.D., and KEVIN T. CLARKE ....336

**Benethamine Penicillin: A New Salt with a Prolonged Action** M. G. NELSON, M.D., M.R.C.P., J. M. TALBOT, M.D., DIP.BACT., and T. B. BINNS, M.R.C.P., D.C.H. ....339

**Assessment of 1,011 Patients in a Mental Deficiency Hospital** GEORGE MCCOULL, M.D., and LEON SLUPINSKI, M.A. 341

**Treatment of Tetanus with Succinylcholine** A. T. T. FORRESTER, M.B. ....342

### MEDICAL MEMORANDUM

Phaeochromocytoma without Hypertension. M. U. HENRY, M.B. ....344

**BOOK REVIEWS** ....345

### GENERAL ARTICLES AND NEWS

RADIOISOTOPES IN MEDICINE ....353
NOVA ET VETERA ....355
REPORTS OF SOCIETIES ....356
MEDICO-LEGAL ....366
MEDICAL NOTES IN PARLIAMENT ....367
UNIVERSITIES AND COLLEGES ....368
MEDICAL NEWS ....372
BIRTHS, MARRIAGES, AND DEATHS ....373
QUESTIONS AND COMMENTS ....373

### OBITUARY

T. W. Letchworth, M.D., F.R.C.S. ....364
Milne McIntyre, M.B., F.R.F.P.S. ....365
F. W. Stuart, M.D., CH.M. ....365
C. E. S. Jackson, M.B., F.R.C.S. ....365
A. H. Elliott, M.B. ....366

**Vital Statistics** ....371

### LEADING ARTICLES

**Blood Groups and Disease** ....347
**Virus Chemotherapy** ....348
**The Artificial Kidney** ....349

### ANNOTATIONS

Illegitimacy and the War ....350
Cancer of the Pancreas ....351
Contact Lenses ....352

### CORRESPONDENCE

A Danger of Surf-bathing. C. LANGTON HEWER, F.F.A. R.C.S. ....358

### SUPPLEMENT

*Full Contents on First Page of Supplement*

**The Work of an Executive Council** ....87
**Ophthalmic Group Committee** ....88
**Correspondence:**
Drugs for Private Patients. E. A. GREGG, M.D.; IAN D. GRANT, M.B. ..88
Dr. Joseph Cort. S. C FERGUSON, L.R.C.P.I., and others .. ....89
Hospital Pharmacy. B. A. YOUNG, M.D. 89

### CORRESPONDENCE—*cont.*

Treatment of Shock. Sir HENEAGE OGILVIE, F.R.C.S.; A. R. JORDAN, F.R.C.S. ....358
Chlorpromazine and Agranulocytosis. J. LOMAS, M.B. ....358
Dashboard Fracture of Patella. R. R. M. PORTER, F.R.C.S.ED. ....359
Harmful Certification. G. C. MILNER, M.B. ....359
Drinking Sea-water. G. R. HERVEY, M.B.; W. S. S. LADELL, M.B. ....359
Isoniazid and Weight Gain. ZWI LARON, M.D. ....360
Dental Extractions for Children. G. H. STUART, F.F.A. R.C.S. ....360
A Mouthful of Wire. MABEL E. CARTER 361
Blood Changes Associated with Disseminated Tuberculosis. W. K. TAYLOR, M.R.C.P. ....361
Fractures Complicating E.C.T. F. H. CORBITT, M.R.C.S. ....361
Familial Paget's Disease. R. E. IRVINE, M.B. ....361
General Practice in America. K. I. E. MACLEOD, M.B. ....361
Coat of Arms. S. F. LOGAN DAHNE, M.D. 362
Child Guidance Clinic. J. BIERER, M.D. 362
*Letters on other subjects appear on p.* 363



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# AUGUST

## THE RIDDLE OF THE SANDS

Some try to do it by standing on one leg and wiggling their spare foot about in the sea. Then they hop, ponderously, a yard or two inland and thrust the foot thus purified into a sock. Provided they do not lose their balance they are soon half-shod. But now they face the even more delicate problem of removing the sand from their remaining toes without wetting the foot which they have just accoutred. A ballet dancer could do it, an acrobat could do it on his head. The average holiday-maker fails.

A more sultanic technique is favoured by those who send small children to fetch water in their little buckets. These citizens carry out their ablutions in comparative comfort; but the buckets represent what planners call an administrative bottleneck, and sometimes, when the tide is out and the children are fractious, this formula will not work. Even when it does, there are still deposits to be removed from between the children's toes.

We are a maritime nation, the heirs of Drake and Frobisher and Nelson. The sea, we are often loosely but emphatically told, is in our blood. How is it that, down the centuries, we have never evolved a satisfactory method of extricating ourselves from this small predicament? Of what flaw in our national character is this failure a symptom? No one knows, and regrettably few care.

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 7 1954

# THE BLOOD GROUPS IN RELATION TO PEPTIC ULCERATION AND CARCINOMA OF COLON, RECTUM, BREAST, AND BRONCHUS

## AN ASSOCIATION BETWEEN THE ABO GROUPS AND PEPTIC ULCERATION

BY

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We have previously shown an association between the ABO blood groups and cancer of the stomach, group A being significantly commoner in patients suffering from cancer of the stomach than in controls drawn from the same hospitals (Aird, Bentall, and Roberts, 1953). The further diseases for which fairly large numbers have so far been obtained are peptic ulceration and carcinoma of the colon, rectum, breast, and bronchus. The results are presented in this paper, which also includes some data on Rhesus grouping. In addition, further calculations have been made on the figures for cancer of the stomach already published. A detailed examination of our data follows. The results have proved remarkably clear-cut: blood group O is strikingly high and the other three groups correspondingly low in patients suffering from peptic ulcer. The three cancers now studied, unlike cancer of the stomach, showed no significant blood-group association.

### Collection of Data

The survey was carried out at 12 hospitals in England, and covers cases treated during the years 1948–53. At the first hospital visited, St. Mark's, London, cases from 1946 were included, but, as the blood groups were not often recorded in the earlier years, surveys in hospitals subsequently visited were restricted to 1948–53. It was also felt that during this period blood-grouping techniques were uniform and reliable.

In such a study it was imperative to have rigid criteria of diagnosis in each disease. For the carcinomas, only cases proved by histological report on material obtained by biopsy, operation, or post-mortem examination were accepted. In peptic ulceration the criterion was a macroscopic report (operation or gastroscopy). The majority of these cases were perforated or bleeding ulcers or those submitted to elective surgery, for it is only in these cases that the blood group is often recorded. Thus our series does not include many medically treated cases and therefore is not representative of all patients suffering from peptic ulceration. Similarly, the majority of the carcinoma cases were those surgically treated.

The same system of collection was used throughout the survey. A member of the team (J. A. M.) visited each hospital and extracted the data directly from the patients' case notes. In all, more than 13,000 case records were scrutinized, and, of these, 7,702 were satisfactory as regards diagnosis and record of blood group. In the final analysis a further small number were eliminated because the patient was suffering from more than one disease. This included in particular 27 patients suffering from peptic ulcer and carcinoma of the stomach or other organs.

For each patient the following items were recorded: disease, subdivision of disease, sex, marital status, age, year of diagnosis, ABO and Rh blood group, occupation, social class, and place of residence. All the information was coded and transcribed to punched cards for analysis. The code is too long for publication, but a copy will be supplied on request. Not all these items have been used for the present paper, but it is hoped to make use of them in the future.

### Selection of Controls

Controls against which to match the blood-group frequencies observed in the different diseases can be selected in two ways. Series for the general populations of the areas concerned may be used, these being usually derived from the records of the National Blood Transfusion Service; or, alternatively, an attempt may be made to secure figures for patients suffering from other diseases at the hospitals concerned. The advantages of the former method are great. Series based on, say, consecutive registrations of blood donors should be unbiased. The numbers available will usually be very much larger than those of the disease groups, so that errors are reduced and smaller differences detected than would otherwise be possible. Moreover, the work has been done already, so that the labour of collecting data is much reduced.

*In receipt of a personal and expense grant from the British Empire Cancer Campaign.

Nevertheless, circumstances could be conceived in which the blood-group frequencies of patients at a particular hospital might differ from those of the area in which it is situated. Hence, while using population controls for the comparisons, it is advisable to see that the hospital populations do not differ significantly from the general population samples. This, however, is easier said than done. In a retrospective survey the groupings available will be confined to diseases in which blood transfusion may become necessary. Some of these may show associations with the blood groups—for example, the cancer of the stomach of the previous paper, or the peptic ulcer of the present investigation. At a general hospital, patients suffering from peptic ulcer form a relatively high proportion of those grouped. At one general hospital which we have investigated it is more than 30%. This is quite enough to explain why most of the hospital controls used in the previous study were too high in O and too low in the other groups, as was then pointed out. Incidentally, it probably also explains the perennial complaint of transfusion officers in large general hospitals that more group O blood is demanded for patients than the proportion of group O in the general population and in the donor pools would justify; moreover, particularly large amounts of blood are often needed by patients suffering from peptic ulcers.

Clearly, then, consecutive series of hospital groupings irrespective of diagnosis cannot safely be used. Undoubtedly the best second-line control is the discovery that at the same centres and the same hospitals certain of the diseases being studied give negative results, yielding frequencies which do not differ significantly from those of the population controls. This is what has happened for three of the diseases included in the present study.

The population control figures used in this paper are given in Table I. The London series is that of Discombe and Meyer (1952), and is based on 10,000 consecutive groupings of pregnant women in North-west London. The figures for Manchester are given by Stratton (1953). Those for Newcastle-upon-Tyne are taken from Roberts (1953), and refer to a count of the National Blood Transfusion panels for Newcastle and Gateshead, as mentioned in the appendix to that paper. The large series, for O and A only, for Leeds, is that of Fisher (Fisher and Roberts, 1943). The smaller complete series for Leeds, as well as those for Birmingham and Liverpool, were kindly provided by the Nuffield Blood Group Centre of the Royal Anthropological Institute.

TABLE I.—*Population Controls Used*

| Area | Group O | Group A | Group B | Group AB |
|---|---|---|---|---|
| London .. | 4,578 | 4,219 | 890 | 313 |
| Birmingham .. | 458 | 442 | 94 | 39 |
| Manchester .. | 4,532 | 3,775 | 788 | 275 |
| Newcastle .. | 6,598 | 5,261 | 1,321 | 392 |
| Leeds .. { | 11,359* | 9,805* | — | — |
| | 983 | 857 | 161 | 61 |
| Liverpool .. | 462 | 402 | 97 | 28 |

* Used for A/O comparisons.

It is interesting to note that for the relative proportions of O and A the two series for Leeds are closely similar, the difference being far below the level of significance. Similarly, Discombe and Meyer's 10,000 for London do not differ significantly from the very large compilation of Fisher and Taylor (1940) for southern England (O, 48,162; A, 45,958; B, 9,059; AB, 3,298). $\chi^2$ for three degrees of freedom is 4.29, or, for O and A only, 2.32 for one degree of freedom. For most of this country large figures for blood-group frequencies are available, and all the indications are that they are accurate within a very small margin of error. Even more complete and systematic mapping will be available later, when further data have been collected by the Nuffield Blood Group Centre as well as by individual workers. The interest of the variations is primarily anthropological, but in addition those concerned with other aspects of blood-group frequencies are fortunate in having available so excellent a body of data against which to match their own series.

## Results

The main basic data are shown in Table II. The chief findings emerge clearly from the summary given in Table III. The control figures are taken from Table I, being weighted in each instance by the numbers in the corresponding disease group in the various areas. In Table III the figures for cancer of the stomach are repeated from the previous paper, though for England only, omitting Scotland. The Scottish sample was drawn from Glasgow, Aberdeen, Perth, and Dundee, and at the moment adequate population controls are not available for what are probably serologically heterogeneous areas.

TABLE II.—*Basic Data*

| Disease | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | O | A | B | AB | O | A | B | AB |
| Gastric ulcer: | | | | | | | | |
| London .. | 187 | 149 | 30 | 7 | 127 | 79 | 16 | 4 |
| Manchester .. | 84 | 58 | 9 | 2 | 38 | 32 | 6 | 3 |
| Newcastle .. | 71 | 42 | 11 | 6 | 31 | 16 | 5 | 2 |
| Total .. | 342 | 249 | 50 | 15 | 196 | 127 | 27 | 9 |
| Duodenal ulcer: | | | | | | | | |
| London .. | 459 | 264 | 59 | 20 | 76 | 47 | 15 | 6 |
| Manchester .. | 190 | 124 | 32 | 12 | 35 | 24 | 5 | 1 |
| Newcastle .. | 254 | 137 | 26 | 6 | 34 | 20 | 4 | 1 |
| Total .. | 903 | 525 | 117 | 38 | 145 | 91 | 24 | 8 |
| Total peptic ulcers*: | | | | | | | | |
| London .. | 696 | 450 | 93 | 30 | 215 | 129 | 31 | 11 |
| Manchester .. | 283 | 188 | 41 | 14 | 78 | 58 | 13 | 4 |
| Newcastle .. | 329 | 183 | 37 | 12 | 67 | 36 | 9 | 4 |
| Total .. | 1,308 | 821 | 171 | 56 | 360 | 223 | 53 | 19 |
| Cancer of colon and rectum: | | | | | | | | |
| London .. | 406 | 407 | 80 | 26 | 259 | 269 | 48 | 19 |
| Birmingham | 136 | 127 | 21 | 11 | 101 | 100 | 19 | 5 |
| Manchester .. | 90 | 72 | 12 | 5 | 73 | 80 | 25 | 2 |
| Newcastle .. | 57 | 49 | 12 | 6 | 42 | 30 | 8 | 2 |
| Total .. | 689 | 655 | 125 | 48 | 475 | 479 | 100 | 28 |
| Cancer of bronchus: | | | | | | | | |
| London .. | 148 | 157 | 36 | 12 | 18 | 5 | 7 | 1 |
| Birmingham | 118 | 102 | 26 | 5 | 10 | 8 | 4 | 1 |
| Manchester .. | 150 | 134 | 33 | 6 | 10 | 6 | 1 | — |
| Total .. | 416 | 393 | 95 | 23 | 38 | 19 | 12 | 2 |
| Cancer of breast: | | | | | | | | |
| London .. | — | — | — | — | 34 | 35 | 11 | 5 |
| Birmingham | — | — | — | — | 232 | 219 | 40 | 11 |
| Manchester .. | — | — | — | — | 155 | 124 | 34 | 12 |
| Newcastle .. | — | — | — | — | 48 | 39 | 17 | 1 |
| Total .. | — | — | — | — | 469 | 417 | 102 | 29 |

* These totals include in addition to the gastric and duodenal ulcers 113 double ulcers, duodenal and gastric, and 32 classified as "prepyloric."

It will be seen that the proportion of patients of group O is greatly increased in peptic ulcer, all the other groups being reduced, and in very nearly the same proportion. The difference in relative proportions of O and A, of O and B, and even of O and AB are all highly significant. Details of the tests of significance for these and other comparisons are given in the Appendix.

It is perhaps surprising that so marked an association was not generally recognized many years ago. In fact, Buchanan

TABLE III.—*Percentage Group Frequencies*

| Group | Peptic Ulcer (3,011 Cases) | | | Cancer of Stomach (2,745 Cases) | | | Cancer of Colon and Rectum (2,599 Cases) | | Cancer of Bronchus (998 Cases) | | Cancer of Breast (1,017 Cases) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Disease | % Inc. or Dec. on Control | Control | Disease | % Inc. or Dec. on Control | Control | Disease | Control | Disease | Control | Disease |
| O | 47·00 | 55·40 | +17·9 | 46·78 | 42·95 | −8·2 | 46·07 | 44·79 | 46·26 | 45·49 | 46·18 | 46·12 |
| A | 40·99 | 34·67 | −15·4 | 41·38 | 46·19 | +11·6 | 41·78 | 43·63 | 41·70 | 41·28 | 41·52 | 41·00 |
| B | 8·98 | 7·44 | −17·1 | 8·79 | 7·76 | −11·7 | 8·94 | 8·66 | 8·79 | 10·72 | 8·93 | 10·03 |
| AB | 3·03 | 2·49 | −17·9 | 3·05 | 3·10 | +1·6 | 3·21 | 2·92 | 3·25 | 2·51 | 3·36 | 2·85 |

and Higley (1921) did discover it. In a series of patients from the Mayo Clinic, suffering from a variety of diseases, gastro-intestinal ulcer stood out as yielding a big excess of group O. They found 122 O's to 55 A's, as compared with 1,024 O's and 933 A's in the rest of their material. The difference is highly significant, $\chi^2$ being 17.3 for one degree of freedom. It is true that grouping errors may have been present at that early date, but there is no reason why they should not have affected the various disease groups equally. Later, Ugelli (1936) found a marked increase in O in a series of 244 patients, and though there was some difficulty over the choice of suitable controls the difference appears to be a true one. Lessa and Alarcao (1949) published a valuable review of the literature. Their own series yielded 227 O's and 217 A's for peptic ulcer, against 813 O's to 1,021 A's among patients suffering from other diseases ($\chi^2$=6.38). These clear indications have tended to be overlooked, partly because of an understandable omission of adequate statistical analysis in the early work, but mainly, perhaps, because the importance of the real difference which had in fact emerged was obscured by discussion of non-significant fluctuations in large numbers of other diseases.

In carcinoma of the stomach A is increased and both O and B are reduced, the differences in the relative proportions of A and O and also of A and B being highly significant. The reduction in B did not emerge in the comparisons of the previous paper, because the hospital controls then used were unduly low in B, probably because of the inclusion of a high proportion of patients with peptic ulcer. The present finding for B agrees with that of Dr. Hollander in the series from Switzerland we then quoted. The rather remarkable result therefore emerges that, while persons of group O are at an advantage in regard to carcinoma of the stomach and persons of group A at a considerably greater advantage in regard to peptic ulcer, in the two diseases for which associations have so far been established persons of group B enjoy both advantages.

In carcinoma of the colon and rectum, in carcinoma of the bronchus, and in carcinoma of the breast there are no significant differences between the disease series and the controls. A preliminary count at an early stage showed a just significant excess of A in carcinoma of the colon and rectum, $\chi^2$ for one degree of freedom being 5. In the final count the difference has become non-significant.

For those who prefer to look at gene frequencies rather than group frequencies, the results of Table III are repeated in Table IV. The gene frequencies are calculated by Fisher's method (Dobson and Ikin, 1946), and the $\chi^2$ for unreasonableness of group proportions is not significant in any disease.

TABLE IV.—*Percentage Gene Frequencies*

| Group | Peptic Ulcer | | Cancer of Colon and Rectum | | Cancer of Bronchus | | Cancer of Breast | | Cancer of Stomach | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Disease | Control | Disease | Control | Disease | Control | Disease | Control | Disease |
| O | 68·5 | 74·6 | 67·8 | 66·8 | 68·1 | 67·0 | 68·0 | 67·7 | 68·4 | 65·5 |
| A | 25·2 | 20·5 | 25·9 | 27·1 | 25·8 | 25·5 | 25·7 | 25·3 | 25·5 | 28·9 |
| B | 6·3 | 4·9 | 6·3 | 6·2 | 6·1 | 7·5 | 6·3 | 7·0 | 6·1 | 5·7 |

Comparisons by sex can be made for peptic ulcer and for carcinoma of the colon and rectum. The numbers of women suffering from carcinoma of the bronchus and, of course, of men suffering from carcinoma of the breast are so small that no sex comparison is possible. In addition, we can add the group frequencies by sex for 1,000 patients with carcinoma of the stomach, drawn from a number of the hospitals of the previous study at which sex was recorded. The total figures are:—men: O, 275; A, 277; B, 61; AB, 20. Women: O, 178; A, 157; B, 22; AB, 10. That the total number should be exactly 1,000 is a coincidence. The findings are summarized in Table V.

TABLE V.—*Percentage Group Frequencies: Sex Comparisons*

| Group | Peptic Ulcer | | Cancer of Colon and Rectum | | Cancer of Stomach | |
|---|---|---|---|---|---|---|
| | ♂ | ♀ | ♂ | ♀ | ♂ | ♀ |
| O | 55·5 | 55·0 | 45·4 | 43·9 | 43·4 | 48·5 |
| A | 34·8 | 34·0 | 43·2 | 44·3 | 43·8 | 42·8 |
| B | 7·3 | 8·1 | 8·2 | 9·2 | 9·6 | 6·0 |
| AB | 2·4 | 2·9 | 3·2 | 2·6 | 3·2 | 2·7 |
| No. | 2,356 | 655 | 1,517 | 1,082 | 633 | 367 |

There is no significant difference in group proportion between the sexes in any of the three diseases. Using totals and comparing the four groups simultaneously, $\chi^2$ for three degrees of freedom is 1.17 for peptic ulcer, 1.95 for carcinoma of the colon and rectum, and 5.22 for carcinoma of the stomach. For carcinoma of the stomach, making the comparison likely to give the most significant difference, as judged by inspection of Table V—namely, O versus the three other groups—$\chi^2$ for the sex difference is only 2.20 for one degree of freedom. Some further sex comparisons are shown in Table IX. The errors are relatively large, however. The 1,000 cases of cancer of the stomach are entirely inadequate for discovering even a relatively large sex difference. The figures do not even exclude the possibility (though it seems very unlikely) that the whole of the excess of A in cancer of the stomach occurs in men. It is striking, however, that in peptic ulcer the figures for men and women should prove so closely similar, and here it does seem that, in spite of the very different incidence of the disease in men and women, the excess of persons of group O is substantially the same in both.

We have made many comparisons within the material, subdividing it in a variety of ways, but without finding any clearly significant difference other than those already mentioned. We say "clearly significant" because two or three differences just significant at the 5% level did emerge; but this is to be expected when several scores of comparisons are made. Duodenal ulcer shows a higher frequency of O than does gastric, but the difference is not significant. (We therefore tested gastric ulcer alone, but found that the excess of O as compared with the controls is still highly significant.) Similarly, there is no significant difference between cancer of the colon and cancer of the rectum. Throughout the material the areas have proved homogeneous for each difference or lack of difference. Some of these finer comparisons are dealt with in the Appendix, together with other details of the analysis.

Finally, age comparisons are also given in the Appendix. For the four diseases (we have no particulars of age in respect of cancer of the stomach) the age distributions for persons of the different groups have been compared, both in total and with various subdivisions—for example, by sex,

area, and subdivision of disease. With one exception no significant association between age and blood groups has appeared. The one exception is that in gastric (not duodenal) ulcer the O's tend to be slightly younger than the A's. But once again this is a barely significant difference and one arbitrarily selected out of many. Age differences may appear in the future when larger numbers are forthcoming; for the moment we can only record a negative conclusion for the data we have.

The figures for the *Rhesus group distribution* (when available) in the diseases studied are given in Table VI. It will be seen that the combined material gives a proportion of Rhesus negatives of 17.2%. This figure is similar to the proportion in the general population of this country. For

TABLE VI.—*Rhesus Group Frequencies*

| Disease | Rhesus Pos. | Rhesus Neg. | Total | % Rhesus Neg. |
|---|---|---|---|---|
| Peptic ulcer .. .. .. | 2,196 | 422 | 2 618 | 16·12 |
| Cancer of colon and rectum | 910 | 219 | 1,129 | 19·40 |
| „ „ bronchus .. | 533 | 103 | 636 | 16·19 |
| „ „ breast .. .. | 773 | 172 | 945 | 18·20 |
| All diseases .. .. | 4,412 | 916 | 5,328 | 17·19 |

$\chi^2$ for heterogeneity, 7·09 for three degrees of freedom.

example, Discombe and Meyer (1952) found the same figure —17.2%—and quote Race's figure of 17.1%. It must be recalled, however, that our data collected from various centres and over a considerable period may be somewhat unreliable owing to minor variations in technique of Rhesus grouping. The differences between the individual diseases are not significant, though the $\chi^2$ for heterogeneity approaches the 5% level of significance.

## Comment

Knowledge of associations between diseases and blood-group frequencies is at an early and empirical stage. There is as yet no prior expectation that a particular disease will show an association. There is no question here of converging lines of evidence, insufficient when taken alone but combining to build up a strong presumption in favour of a particular hypothesis. In these circumstances the assumption must be that there is no association until strong evidence is forthcoming which refutes this null hypothesis. It will probably be further agreed that something much stronger than conventional borderline probabilities is needed before results are accepted as more than an indication for the collection of more data. There are several reasons which reinforce this view. For example, there must usually be some doubt about the appropriateness of the control sample used. There may be a small margin of error, which as often as not will inflate the difference. To take another point, when many comparisons are made some must give low probabilities by chance; and if these are singled out without allowing for the fact that they are a few arbitrarily selected from many, the existence of associations will be too readily accepted.

Moreover, it is not only a question of a disease taken as a whole. Subdivisions of the disease may be made, as well as subdivisions by sex, by age, or in other ways. If, taking a disease or disease group as a whole, and taking all patients together, there is no evidence of association, the presumption, unless it is refuted by strong evidence, is that no further subdivision will reveal an association.

The appropriate null hypothesis for subdivisions where a clear association has emerged from the data taken as a whole are not quite so obvious. Presumably, in, say, peptic ulcer, the null hypothesis to be tested is that the increase in O is equal in the two sexes, though here more conventional levels of significance seem appropriate. Again, as both the allied diseases, duodenal and gastric ulcer, show a highly significant rise in O, it is assumed that the rise is the same unless there is a significant difference between them. For age comparisons, the null hypothesis is that there is no difference between patients of the different groups unless there is evidence to the contrary.

The desirability of caution in drawing deductions in this new field of inquiry further emphasizes the numbers needed for the detection even of large differences. If our series is typical, a person of group O is about 35% more likely to develop peptic ulcer (requiring treatment in hospital) than are persons of the other groups. Yet to produce strong evidence that there is an association would require, say, 500 patients if the control series was very large or about 1,000 with a control series of equal numbers. The smaller, though considerable, association in cancer of the stomach could hardly be established with a number substantially less than our 2,700 patients for England. When we turn to subdivisions the difficulties multiply, for not only are the numbers reduced, often into unequal fractions, but they now have to be compared with each other instead of with large population control series.

It is certainly desirable that the relationship between the blood groups and various diseases should be further explored, as indeed it is being explored in many parts of the world. It is also highly desirable to examine subdivisions of various kinds, but very large numbers are required. It is unlikely that any one centre, or even any one country, can furnish sufficient numbers of the rarer diseases or of some of the subdivisions of the commoner ones. There is good reason, therefore, for the publication of series which, though not individually adequate for analysis, can be added to others when sufficient of them are placed on record. It is important that papers published now should avoid the inadequacy of earlier series, an inadequacy which for many years threw this kind of research into disrepute. A survey of the earlier literature shows clearly what these errors are. They include inaccuracy of diagnosis, inadequacy of controls, and the examination of vague clinical or pathological entities, the grouping of unrelated diseases together on the one hand, and the subdivision of diseases into vague and unacceptable groups on the other. If relatively small series are to be collected and reported it would seem important to limit the data to precise pathological entities of a clear-cut kind, whose recognition is likely to be standard throughout the world. Comparison between different series will be possible, and the conclusions based on individual series valid, only if diagnosis is precise and expressed in terms which meet with general acceptance. It is to be hoped, however, that when small series are published restraint will be shown in not complicating the literature with too much discussion of differences which so far are of no significance or of doubtful significance.

Turning to the interest of the present findings in the general field of biology, the outstanding point is the demonstration that the blood groups do in fact have selective value. Following the work of such pioneers as Fisher and Ford, it has long been clear (for the ABO groups in particular) that a polymorphism which is probably as old as the species could have persisted only provided that mechanisms are at work which favour a balance between the allelomorphic genes. With few exceptions all human communities have appreciable amounts of the three genes, O, A, and B; the exceptions, such as the absence of B in the aboriginal population of South America, may well be due to colonization by small groups in whom that gene happened to be lacking or was not perpetuated. No doubt the balance changes, but at least it does not appear that the unconditional advantages or disadvantages are ever such that any of the genes disappear.

While, however, it has been predictable that the different combinations of the blood-group genes would be found to possess balancing advantages and disadvantages, most biologists would probably have expected that these were to be sought in small differences in traits of high survival value, manifested in the selective elimination of foetuses, or in differential death rates before reproductive age is reached. There is, indeed, evidence of such things, for

example, in Hirszfeld and Zborowski's (1926) observation that there are fewer offspring from the mating O mother by A father than in its reciprocal, A mother by O father—a view for which some further evidence has been produced by Waterhouse and Hogben (1947). These and similar ideas have been further developed by Allan (1953). Nor should it be forgotten that in peoples amongst whom Rhesus negatives occur, incompatible ABO matings confer a great advantage in regard to haemolytic disease. After birth there is the observation of Struthers (1951) that an excess of A children, as against O, die of bronchopneumonia during the first two years of life.

What is rather surprising, perhaps, is to find relatively very large associations with diseases of middle and late life, diseases of distinctly low selective value. Nevertheless, even if cancer of the stomach is a disease of late onset, which cannot be expected to have much effect on reproductive rates, peptic ulcer cannot be of negligible import in this respect. Many patients develop their ulcers quite early in life and the mortality is not inappreciable. The extent to which peptic ulcer lessens the likelihood of marriage and a family is more speculative, though it seems likely that reproductive rates are at least somewhat lowered (we reject the hypothesis that marriage and a family are the cause of the ulcers). With so great an association as has emerged in this inquiry, it is clear that even if the selective value of peptic ulcer is no more than moderate it is likely to be a not unimportant factor in the balance.

The two diseases, cancer of the stomach and peptic ulcer, are, however, only two factors out of a number which is likely to be large. An indication of this is seen in the fact that for these two diseases, persons of group B are at an unqualified advantage in both. There may well be other factors of prenatal and early life which redress the balance, as well as associations yet to be discovered with other diseases.

One mechanism for preserving a polymorphism is for the heterozygote to have a selective advantage. It is true that all O's, the group most affected by peptic ulcer, are homozygotes, whereas (in this country) 5 out of 6 A's are heterozygous, together with 29 out of 30 B's and all the AB's. In cancer of the stomach, however, it is the proportion of the mainly heterozygous, the A's, which is increased.

The fact that associations have been found with diseases of adult life—indeed, of middle and old age—brings the blood groups squarely into the general medical field. In the hazards of transfusion and in haemolytic disease of the foetus and newborn the association with the blood groups is dependent upon antigen-antibody reaction; this might also prove to be true of the association between blood group and toxaemia of pregnancy shown by Pike and Dickins (1954) in a paper published elsewhere in this issue. It by no means follows, however, that the association between gastric disease and blood groups, or the association, if it is proved, between blood groups and bronchopneumonia of young children (Struthers, 1951), is due to this antigen-antibody reaction.

Two possibilities may be disposed of at this point. Any explanation inculpating the antibodies themselves as active chemical agents either in the production of peptic ulceration or in carcinogenesis seems unlikely, as the antibodies occurring in groups A and B are both present in group O. The second is the suggestion that blood groups may be changed by cancer. In an annotation in the *British Medical Journal* (1953) the following statement appears: "The validity of this conclusion" (that blood groups have a selective value) "depends on the validity of the assumption that a blood group can never be changed by cancer or extrinsic factors causing cancer. This cannot be regarded as certainly true until it has been properly tested; and if it should prove incorrect an explanation of the statistical relationship might be found in a common cause." There is no known evidence of a change in the blood group of an individual due to cancer or any other cause, and all the known facts contradict the possibility of such an occurrence. During the course of very large numbers of repeated transfusions, and, even more, of repeated donations of blood by millions of donors, surely such a remarkable phenomenon would have come to light. We feel, therefore, that the suggestion that blood groups may change does not merit further consideration.

It is indeed difficult to elaborate any hypothesis which will explain why possession of blood group O should predispose to the development of peptic ulceration while the possession of blood group A should predispose to cancer of the stomach. It is equally difficult to understand why the possession of blood groups A and B should protect against peptic ulceration while possession of blood groups O and B should protect against carcinoma of the stomach. Blood groups A, B, and AB depend upon the presence of relevant A and B substances which are endowed, perhaps fortuitously, with antigenic properties. Chemically these blood-group substances are classified as mucopolysaccharides. These have been distinguished from each other only by their antigenic properties and, more recently, by minor chemical differences. There does not appear to be a specific group substance for the blood group O, as no serum has been proved to react specifically with the product of the O gene. Those who belong to group O are provided with a mucopolysaccharide called H substance, but this appears also to be present to a less extent in people who belong to the other blood groups. These specific mucopolysaccharides are present in small quantities in relation to the red corpuscles of the blood, but they appear in body tissues and fluids in very much larger quantities (Morgan, 1944). In the majority of people they occur in digestive secretions. The stomach wall seems to be rich in these group substances.

The simplest, though not necessarily the most acceptable, explanation of our findings would be the assumption that A substance is carcinogenic with respect to the stomach while both A substance and B substance protect against peptic ulcer. In the light of what is known of chemical carcinogenesis it would be difficult to incriminate the mucopolysaccharides as active agents in the genesis of carcinoma. From what is known of these substances it would be more plausible to think of some kind of protective action exercised by one or other of the polysaccharides against those influences, including hyperacidity, which are known to produce peptic ulceration, and those hypothetical carcinogens which, presumably exerting their action from the lumen of the stomach, may contribute to the environmental factor which Stocks (1950) has postulated. It might be crucial in deciding this question to know whether the secretion of A substance protects against peptic ulceration more effectively than does its mere presence in the blood, and we are collecting data of the incidence of cancer of the stomach and of peptic ulceration in secretors, but the accumulation of data is slow. Further examination of the mechanism of the relationship between the blood groups and these two diseases, peptic ulcer and cancer of the stomach, would be accelerated by direct laboratory experiment, but the separation of the blood-group substances even in tiny amounts is difficult and laborious, and it would perhaps be unwise to draw any conclusions now other than that the blood-group substances might exercise some important gastric function.

## APPENDIX

### 1. Combination of Data from Different Areas

The material analysed in this paper was drawn from several areas having differing blood-group frequencies in their general populations. What is required is a single combined estimate of each difference studied, with a test of its significance, and also a test to show whether the various areas are homogeneous or not in regard to the overall difference. This problem often arises in work on the blood groups, and will no doubt do so even more often in the future, when individual series for various diseases are published, each too small for any conclusion, though adequate for analysis when added together. No doubt, too,

TABLE VII.—*Combination of Areas: Peptic Ulcer, A/(A+O)*

| Centre | Peptic Ulcer | | Population Control | | A/(A+O) | | | Weight (w) |
|---|---|---|---|---|---|---|---|---|
| | O | A | O | A | Ulcer ($p_1$) | Control ($p_2$) | Ulcer-Control ($p_1-p_2=d$) | |
| London .. .. .. | 911 | 579 | 4,578 | 4,219 | 0·388591 | 0·479595 | −0·091004 | 5,324·1 |
| Manchester .. .. | 361 | 246 | 4,532 | 3,775 | 0·405272 | 0·454436 | −0·049164 | 2,342·3 |
| Newcastle .. .. | 396 | 219 | 6,598 | 5,261 | 0·356098 | 0·443629 | −0·087531 | 2,540·4 |

Sw = 10,206·8

it will often be desirable to combine series from different countries, with distinctly different blood-group frequencies. Except for the rather artificial special case in which the numbers in the disease group and the control group are in the same proportion, or practically so, in each area, simple addition of the frequencies will not yield a correct estimate of the combined difference, or lead to valid tests of significance. To take an unweighted average of the differences in proportion between the disease and control series is inefficient because it does not allow for differences in the accuracy of these proportions. What is required is to give the difference in proportion for each area a weight which is inversely proportional to its estimated variance. The procedure is illustrated for the relative proportions of O and A in peptic ulcer as compared with the control series, and the calculations are shown in Table VII.

If in each area $n_1$ is the number of O's and A's in the peptic ulcer series, giving a proportion A/(A+O) of $p_1$; $n_2$ and $p_2$ are the corresponding figures for the controls; then the weight, w, for that area is:

$$1\Big/\left(\frac{p_1q_1}{n_1}+\frac{p_2q_2}{n_2}\right)$$

where $p_1+q_1=1$, and $p_2+q_2=1$. The difference is $p_1-p_2=d$, and the combined weighted mean difference for all areas is Swd/Sw; $\chi^2$ for the difference, with one degree of freedom, is $(Swd)^2/Sw$; $\chi^2$ for the homogeneity of the areas is $Swd^2-(Swd)^2/Sw$, with degrees of freedom one less than the number of areas.

The weight for London, for example, is:

$$1\Big/\left\{\frac{(0.3885906)\,(1-0.3885906)}{(911+579)}+\frac{(0.4795953)\,(1-0.4795953)}{(4,478+4,219)}\right\}$$
$$=5,324.06$$

The weighted mean difference is −0.08054; $\chi^2$ for this difference is 66.21 with one degree of freedom; $\chi^2$ for heterogeneity is 3.01, with two degrees of freedom.

In Table II of the previous paper on cancer of the stomach a simpler procedure was set out, though the results using the method of this section were also stated. We hope that no one will be misled by that table, and would emphasize again that the simpler procedure was applicable only because the disease group and the controls were practically equal in number at each centre.

## 2. Significance of the Differences

With the ABO blood groups it is possible to examine simultaneously the variation in all four group frequencies, or in all three gene frequencies. For a number of practical purposes, however, it seems more appropriate, and is certainly much simpler, to make single comparisons—that is, to examine separately, for example, the relative proportions of groups O and A, or of O and B, or of O against the sum of the other three. In particular, the O and A comparison is often the only one for which the numbers are sufficient, and it may then seem unnecessary to complicate the analysis with groups B and AB. Hence most of the comparisons of this paper have been made in this simple way. Those for each disease taken as a whole, using the method described in the first section of the appendix, are shown in Table VIII. It will be noted that all the areas are homogeneous for each difference, except that for the comparison of A and B for cancer of the stomach the $\chi^2$ just attains the 5% level of significance.

TABLE VIII.—*Significance of Main Comparisons. Weighted Mean Differences and Homogeneity of Areas*

| Disease | Ratio Examined | Weighted Mean Difference (Dis.−Con.) % | $\chi^2$ for Difference (D. of F. =1) | Heterogeneity of Areas | |
|---|---|---|---|---|---|
| | | | | D. of F. | $\chi^2$ |
| Peptic ulcer .. | A/(A+O) | −8·05 | 66·21 | 2 | 3·01 |
| ,, ,, .. | B/(B+O) | −4·31 | 29·06 | 2 | 3·81 |
| ,, ,, .. | AB/(AB+O) | −1·75 | 10·96 | 2 | 0·68 |
| Cancer of colon and rectum .. | A/(A+O) | +1·87 | 2·73 | 3 | 1·03 |
| Cancer of bronchus | A/(A+O) | +0·33 | 0·03 | 2 | 1·03 |
| ,, ,, breast | A/(A+O) | −0·29 | 0·02 | 3 | 0·34 |
| ,, ,, stomach | A/(A+O) | +4·93 | 21·49 | 5 | 2·69 |
| ,, ,, ,, | B/(B+A) | −3·83 | 16·47 | 5 | 11·46 |

Some of the comparisons for subdivisions of the peptic ulcer series are set out in Table IX. No difference is significant, though, as already pointed out in the text, the numbers are distinctly small when subdivisions are made.

TABLE IX.—*Further Tests of Significance for the Ratio A/(A+O) Within the Peptic Ulcer Series*

| Comparison | Weighted Mean Difference % | $\chi^2$ for Difference (D. of F. =1) | $\chi^2$ for Heterogeneity of Areas (D. of F.=2) |
|---|---|---|---|
| (Gastric ulcer)–(duodenal ulcer) | +3·82 | 3·58 | 0·78 |
| (Gastric ulcer ♂)–(gastric ulcer ♀) | +3·13 | 0·85 | 1·66 |
| (Duodenal ulcer ♂)–(duodenal ulcer ♀) .. .. .. | −1·65 | 0·23 | 0·01 |
| (Gastric ulcer)–(controls) .. | −5·63 | 11·49 | 1·02 |

It may be that larger series will show that there is a difference in blood-group frequencies between gastric and duodenal ulcer, and other differences may also emerge, but all that can be done at present is to record negative conclusions on the data available.

## 3. Age

The frequency distributions of ages by disease, sex, and blood group have been analysed for the four diseases treated in this paper, omitting the small number of women with

TABLE X.—*Mean Ages, with Standard Errors, by Blood Group and Sex*

| Group | Gastric Ulcer | | | | Duodenal Ulcer | | | | Cancer of Colon and Rectum | | | | Cancer of Bronchus | | Cancer of Breast | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | Females | | Males | | Females | | Males | | Females | | Males | | Females | |
| | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. |
| O | 52·19 | 0·63 | 55·20 | 0·90 | 47·11 | 0·43 | 49·60 | 1·11 | 61·07 | 0·44 | 59·67 | 0·55 | 54·05 | 0·41 | 54·33 | 0·53 |
| A | 54·15 | 0·69 | 56·48 | 1·16 | 46·78 | 0·56 | 47·66 | 1·31 | 61·03 | 0·48 | 60·32 | 0·54 | 53·82 | 0·41 | 54·92 | 0·60 |
| B | 52·50 | 1·44 | 52·13 | 2·64 | 45·24 | 1·19 | 49·58 | 2·15 | 62·46 | 1·09 | 58·90 | 1·28 | 53·97 | 0·97 | 55·78 | 1·18 |
| AB | 50·50 | 3·80 | 50·28 | 4·09 | 43·42 | 1·77 | 58·13 | 5·21 | 60·00 | 1·40 | 57·32 | 1·85 | 55·33 | 1·60 | 52·50 | 2·34 |

*Note.*—Numbers as in Table II.

cancer of the bronchus. We have no data for cancer of the stomach. Making a number of comparisons, including a variety of further subdivisions, and also of additions, only one barely significant difference emerges. It was noted that in both sexes and in all three areas patients of group A with gastric ulcer were older than patients of group O. Simple addition of the figures gave a difference of 1.64 years, 2.05 times its standard error. Simple addition is not adequate, but, using a method of weighting analogous to that used for the group comparisons, the result was unchanged. This difference, however, is only one arbitrarily selected out of many, and there is no confirmation in the figures for duodenal ulcer, nor in those of groups B and AB. The conclusion is, therefore, that, both in the disease which shows blood-group associations—peptic ulcer—and in the three giving a negative result, there is no evidence on these numbers of any difference in mean age between patients of the four groups. Table X shows mean ages with their standard errors for the most important subdivisions.


### Summary

Data are presented on the ABO blood-group frequencies amongst 3,011 patients with peptic ulcer, mainly those who have required treatment by transfusion and/or operation, 2,599 with cancer of the colon and rectum, 998 with cancer of the bronchus, and 1,017 with cancer of the breast.

Compared with controls from the general population of the areas sampled, patients suffering from peptic ulcer show an increased incidence of group O and a correspondingly lower incidence of the other three groups. The difference is a large one. If our series is typical, persons of group O are about 35% more likely to develop peptic ulceration than are persons of the other groups.

The ABO frequencies shown by the three cancers do not differ significantly from the population controls. These three negative results serve as a test of the appropriateness of using population controls for hospital patients.

On the numbers available, there is no indication of any difference in ABO frequencies between gastric and duodenal ulcer.

In none of the diseases is there any significant difference in sex proportion or in age between patients of the four blood groups.

Patients suffering from the four diseases do not differ significantly in the proportion who are Rhesus negative, the overall value being close to the expectation in the general population.



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# ABO BLOOD GROUPS AND TOXAEMIA OF PREGNANCY


BY

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The advantages and disadvantages of belonging to one or other ABO blood group are being slowly established. Aird, Bentall, and Roberts (1953) have shown the disadvantage of group A in cancer of the stomach, and Aird *et al.* (1954) that of group O for peptic ulcers. There was an excess of group A children dying under 2 years of age from bronchopneumonia (Struthers, 1951); and fertility and abortions (Waterhouse and Hogben, 1947; Allan, 1953) also show differing incidence in the various blood groups. It occurred to one of us (L. A. P.) that toxaemic and non-toxaemic patients could be compared in this respect in relatively large numbers from existing obstetric records.

### Material

The investigation was carried out on 3,813 consecutive admissions to Perivale Maternity Hospital between March, 1951, and April, 1954. Primigravidae are booked in order of their application for admission, to the extent of available beds, and constituted almost half the admissions. Multiparae are admitted on medical, obstetrical, and social grounds only. Dr. J. R. E. Richardson, of the King Edward Memorial Hospital, Ealing, has been responsible for the routine grouping of all patients.

A patient was regarded as toxaemic if she possessed two of the following signs: (1) a blood pressure of 140/90 or

over, after the 28th week of pregnancy; (2) the presence of clinical oedema, or a weight gain of more than 1 lb. (450 g.) a week during the same period; (3) the presence of albuminuria in a catheter specimen, not due to infection. These criteria eliminate those few chronic hypertensive patients who did *not* develop "superadded toxaemia" by showing oedema or albuminuria. The others (the majority) are included. No case of chronic nephritis was admitted during the period studied. Only two patients developed oedema and albuminuria without a hypertension of 140/90.

A few cases of abortion were omitted, together with some for whom the records were incomplete. The total omitted was 162, leaving 3,651 acceptable records.

These records are included in a larger compilation of 10,000 pregnant women made by Dr. J. R. E. Richardson, who has kindly allowed us to use his figures.

## Results

The distribution of groups in our series of 3,651 cases and in Dr. Richardson's larger series proved very similar to those of Discombe and Meyer's (1952) 10,000 pregnant women drawn from an area of Middlesex adjacent to our own (Table I). All three series agree very closely. Comparing our series and Richardson's larger series with that of Discombe and Meyer, $\chi^2$ for three degrees of freedom was respectively 3.17 and 0.40.

TABLE I.—*Group Frequencies in Totals of Pregnant Women*

| Group | Present Series | | Richardson's Series | | Discombe and Meyer's Series | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| O | 1,706 | 46·73 | 4,579 | 45·79 | 4,578 | 45·78 |
| A | 1,545 | 42·32 | 4,238 | 42·38 | 4,219 | 42·19 |
| B | 297 | 8·13 | 866 | 8·66 | 890 | 8·90 |
| AB | 103 | 2·82 | 317 | 3·17 | 313 | 3·13 |
| Total .. | 3,651 | | 10,000 | | 10,000 | |

There is a marked preponderance of group O in the toxaemic patients (Table II). Comparing the relative proportions of group O and the other groups taken together, for toxaemic and non-toxaemic patients the difference is highly significant ($\chi^2$, with Yates's correction, is 11.75). Comparing the proportions of groups O and A only, $\chi^2$ is 9.09—again significant—and a comparison of group O against B, despite the fact that the number of the latter is small, gives a $\chi^2$ of 5.35.

TABLE II.—*Group Frequencies in Toxaemic and Non-toxaemic Patients*

| Group | Non-toxaemic Patients | | Toxaemic Patients | | % Increase or Decrease of Toxaemic Patients Over Non-toxaemic Patients |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| O | 1,416 | 45·5 | 290 | 53·6 | +18 |
| A | 1,342 | 43·2 | 203 | 37·5 | −13 |
| B | 263 | 8·5 | 34 | 6·3 | −26 |
| AB | 89 | 2·9 | 14 | 2·6 | −10 |
| Total | 3,110 | | 541 | | |

It was thought important to find whether these differences were predominantly due to primigravidae or to multiparae, but no such effect was found ($\chi^2$ for three degrees of freedom is 2.67). As stated above, the total admissions over the period studied comprised primigravidae and multiparae in almost equal numbers. Table III does not show the expected preponderance of primigravidae in toxaemic patients, but it must be remembered that the multiparae were a group selected for hospital confinement.

TABLE III.—*Group Frequencies by Parity in Toxaemic Patients*

| Group | Primigravidae | | Multigravidae | |
|---|---|---|---|---|
| | No. | % | No. | % |
| O | 146 | 51·8 | 144 | 55·6 |
| A | 106 | 37·6 | 97 | 37·5 |
| B | 22 | 7·8 | 12 | 4·6 |
| AB | 8 | 2·8 | 6 | 2·3 |
| Total | 282 | | 259 | |

## Discussion

This increased proportion of group O patients developing toxaemia of pregnancy, with the increased risk of foetal loss that toxaemia implies, is interesting from many points of view. If proved typical it must be remembered when considering stabilizing mechanisms for maintaining the distribution of blood groups. It might prove to account in part for the shortage of A children from the mating of O mothers with A fathers, shown by Waterhouse and Hogben (1947).

The problem arises whether the association might be due in some way to ABO incompatibility between foetus and mother. Harvey Smith (1945) found that mothers carrying a heterospecific foetus (that is, a foetus bearing a blood-group antigen of the ABO system absent from the maternal red cells) showed distinct evidence of iso-immunization in the second half of pregnancy, and in most cases the rise in antibody titre persisted into the puerperium. He did not mention whether his subjects suffered from toxaemia or not. This effect was shown only when the babies were secretors of group-specific substance (and could therefore presumably transmit antigen through the placenta, without the actual passage of foetal red cells). Group O mothers have a greater chance than those of other groups of bearing a heterospecific foetus. In a population with group frequencies such as those shown in Table I, about 32% of O mothers will bear a heterospecific foetus, as against about 6% for A mothers.

Dienst (1905) made the surprising statement that "eclampsia is nothing but a transfusion of incompatible blood of the child into the mother's circulation as a result of a communication between the two." He abandoned this idea (Dienst, 1908) for what seem rather inadequate reasons, but it was resurrected and elaborated by McQuarrie (1923) and Ottenberg (1923). It was then severely criticized by Allen (1926) and again passed into oblivion. With further interest, however, in iso-immunization and its association with foetal loss, Schwartz and Levine (1943), Browne (1944), and Harvey Smith (1945) have all suggested that further work on the association of ABO blood groups and toxaemia is necessary. Perhaps their advice should be taken and the situation reassessed.

In some cases certain of the features of toxaemia might conceivably be explained by a variety of antigen–antibody reaction, either in the blood or in the walls of the smaller vessels of the mother. Most of the toxaemic phenomena are essentially vascular. Oedema, albuminuria, anuria and oliguria, hepatic and cerebral changes, have been thought to be associated with vascular damage, and toxaemic hypertension is humoral, not neurogenic, in mechanism (Kellar and Sutherland, 1941). Placental insufficiency has been demonstrated by many ingenious methods, and is thought to be due to some interference with the maternal blood supply. No existing theory of the aetiology of toxaemia known to us can explain the appearance of eclampsia or a continued rise in blood pressure in the puerperium, but Harvey Smith and Dienst found the rise in antibodies to persist at least until the fourth day of the puerperium (although their observations at that time were few).

It is obvious that this mechanism is not a factor in many cases of toxaemia. For instance, our figures show 14 toxaemic patients belong to group AB who cannot have carried heterospecific foetuses as defined by Levine (1946). Dr. Richardson has kindly looked up records of 33 toxaemic rhesus-negative mothers, and finds that only four children were heterospecific, and two possibly heterospecific. It would, moreover, need more armchair ingenuity than we possess to explain the known hormonal changes in toxaemia.

But it should be possible to prove or disprove whether this mechanism is a factor in some cases of toxaemia, and further work is planned.

There is another way of looking at this problem. Browne and Dodds (1939) showed that about 50% of toxaemic patients were left with a residual hypertension. They were at that time using a blood pressure of 130/70 as a criterion for both conditions. Other workers, using higher blood pressures as criteria, have shown proportionately similar results. Nevertheless, Isenhour, Kuder, and Dill (1942) have shown no increased incidence of hypertension (140/90) in parous rather than in nulliparous patients, and conclude that hypertension following toxaemia occurs in those patients who would have developed it in any case. Perhaps, however, toxaemia in the other group—those not destined to develop permanent hypertension—could be due to a mechanism peculiar to pregnancy such as we have postulated. It would be interesting to know the group distributions in chronic hypertension.

Any discussion on this subject must remain highly speculative; nevertheless, if these empirical findings are confirmed in other series some explanation must be sought.


### Summary

The distribution of blood groups in 3,651 admissions to a maternity hospital has been studied. These admissions included 541 patients suffering from toxaemia of pregnancy.

As compared with the non-toxaemic patients, the toxaemic patients showed a significant excess of women of group O.

Some possible implications are discussed.


We are indebted to Dr. J. A. Fraser Roberts for advice and help with the statistical analysis. We are grateful to Mr. H. H. Bentall and Dr. J. A. Mehigan, of the Department of Surgery, Postgraduate Medical School of London, for their continued interest and help, and to them and to Dr. P. L. Mollison for discussions on the possible role of iso-immunization. Our great indebtedness to Dr. J. R. E. Richardson has already been mentioned in the text.

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Professor A. B. SEMPLE, medical officer of health of Liverpool, in his annual report for 1953 remarks that there was some disquiet about the standard of food hygiene in Liverpool, and that detailed inspection suggested that co-operation was not being maintained by some managements and by personnel employed in some food establishments. "Day-to-day cleanliness was not carried out satisfactorily and many employees were careless in their habits, and the absence of soap, towels, and hot water made things worse. Large accumulations of dirt were found as well as major infestations of rodents and pests." Eventually legal action was taken against the managements of eight bakehouses and eleven cafés. All were found guilty, 15 of the 19 defendants pleading guilty in court.

# BLOOD GROUPS IN CARCINOMA OF THE LUNG


BY

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This inquiry into the distribution of the ABO and rhesus blood groups in carcinoma of the lung was prompted by the recent paper by Aird and his colleagues (1953); they found a statistically significant association between cancer of the stomach and blood group A, suggesting that there may be some factor in the disease which is inherited. In lung cancer, on the other hand, a great deal of new work stresses the environment, and there is good evidence of a connexion between this carcinoma and cigarette smoking (Wynder and Graham, 1950; Doll and Hill, 1952; McConnell *et al.*, 1952). On *a priori* grounds an external factor such as tobacco is likely to account for the recent rapid increase in the incidence of carcinoma of the lung, since a mutant gene could not possibly have spread through the population in such a short space of time. Nevertheless, a large number of people who smoke heavily do not develop the disease, and as many as 40.5% of the cancer patients of Doll and Hill (1952) had smoked less than the equivalent of 16 cigarettes a day. Experiments with mice suggest that some strains are more susceptible than others to carcinogens, and it may be that in man part of the population has an inborn tendency to cancer. It therefore appeared worth while investigating the blood groups of cases of cancer of the lung to see if these provided any support for the presence of an inherited factor.

### Sources of Material

The 777 patients with cancer of the lung which form the basis of this paper were all drawn from the records of the Liverpool Thoracic Surgical Unit. During the years 1944–53 about 2,000 cases of lung cancer were diagnosed by the unit, and all the histologically proved cases which had been blood-grouped have been included in this series. The histological proof of the disease was from biopsy of the growth, operation specimens, or post-mortem material.

In other surveys of this nature blood-groupings done before 1948 have not been included, on the ground that the standard of technique was not uniformly good up to then. This series includes ABO cases from 1944 onwards, as it is felt that the standard of grouping was high enough throughout and the majority of the earlier cases which were grouped were operated upon and received blood transfusions. The rhesus groupings date from 1949.

As a control, the blood-group distribution amongst 1,000 blood donors of the Liverpool Regional Blood Transfusion Service has been used. In order to avoid any bias due to people who know that they are rhesus negative and therefore volunteer as blood donors, only those being grouped for the first time were included. Samples were drawn over the whole area covered by the Blood Transfusion Service—that is, from North Wales, West Cheshire, and West Lancashire; this is the same area from which the Regional Thoracic

Surgical Centre draws its patients. This control group seems very satisfactory in every way except that it applies to the population as in 1953–4, whilst the cancer patients were seen in 1944–53; however, it is unlikely that any population shift which has occurred during the past few years would have had any appreciable effect on the blood-group distribution in the population of the area.

*Classification of Material.*—The cancer cases were divided into the following histological subgroups: (1) squamous and transitional cell; (2) oat and oval cell; (3) undifferentiated, anaplastic, carcinoma simplex, spheroidal and polygonal cell; (4) adenocarcinoma and columnar cell; (5) "mixed" cell tumours and unclassified. Pathologists vary greatly in their methods of classification of lung tumours, but in this series the histology of the great majority of the cancers was reported on by one pathologist, and only some of the earlier cases were dealt with by another. There are good grounds for believing that the terms "oat" and "oval" were used respectively by them to describe the same type of cell, and these have therefore been put together in the second subgroup.

## Results

The findings are analysed in the accompanying Tables.

Taking all the 777 lung cancer cases together, we find that their ABO blood-group distribution shows no significant difference from the control group (Table I). $\chi^2=1.43$ with three degrees of freedom.

TABLE I.—*Distribution of ABO Blood Groups in 777 Lung Cancer Cases Compared with 1,000 Controls*

| Blood Group | Cancer Cases | | Controls | |
|---|---|---|---|---|
| | No. | % | No. | % |
| A | 312 | 40·15 | 406 | 40·60 |
| B | 55 | 7·08 | 81 | 8·10 |
| AB | 31 | 3·99 | 32 | 3·20 |
| O | 379 | 48·78 | 481 | 48·10 |
| Total.. | 777 | 100·00 | 1,000 | 100·00 |

TABLE II.—*Distribution of ABO Blood Groups for the Different Histological Types*

| Histological Type | Blood Group | | | | Total |
|---|---|---|---|---|---|
| | A | B | AB | O | |
| Squamous cell .. .. | 131 | 29 | 16 | 186 | 362 |
| Oat cell .. .. .. | 96 | 11 | 8 | 86 | 201 |
| Undifferentiated .. .. | 54 | 7 | 6 | 65 | 132 |
| Adenocarcinoma .. .. | 13 | 2 | 0 | 19 | 34 |
| Mixed .. .. .. | 18 | 6 | 1 | 23 | 48 |
| Total .. .. | 312 | 55 | 31 | 379 | 777 |

TABLE III.—*Analysis of Differences of Relative Proportions of Groups O and A in Cancer Cases and Controls for Different Histological Types*

| Histological Type | Cancer Cases | | Controls | | A/(A+O) % | | Diff. | $\chi^2$ |
|---|---|---|---|---|---|---|---|---|
| | A | O | A | O | Cancer | Control | | |
| Squamous cell .. | 131 | 186 | | | 41·32 | | +4·45 | 1·87 |
| Oat cell | 96 | 86 | | | 52·75 | | −6·98 | 2·95 |
| Undifferentiated | 54 | 65 | 406 | 481 | 45·38 | 45·77 | +0·39 | 0·01 |
| Adenocarcinoma | 13 | 19 | | | 40·62 | | +5·15 | 0·33 |
| Mixed .. | 18 | 23 | | | 43·90 | | +1·87 | 0·06 |
| Total .. | 312 | 379 | 406 | 481 | 45·15 | 45·77 | +0·62 | 0·06 |

The last column contains values of $\chi^2$ calculated from the individual 2×2 tables.

*Analysis*

| | D. of F. | |
|---|---|---|
| Sum of $\chi^2$ for the different histological types .. | 5 | 5·22 |
| Total for all types .. .. .. .. | 1 | 0·06 |
| Difference due to heterogeneity .. .. .. | 4 | 5·16 |

These figures give no evidence of heterogeneity. Comparing the A:O distribution of the oat-cell type with that of the sum of all others gives a significant result ($\chi^2=5.76$ with 1 d.f.). This may represent a real difference in the oat-cell type; but one extreme value in five is not an improbable occurrence, and this last analysis is in effect picking out this extreme value (see also text).

The ABO blood-group distribution in all the histological subdivisions is normal, except in the oat-cell and oval-cell tumours (Table II). In this group there is an increase in the number of group A at the expense of group O, and this increase holds if the oat and oval cells are analysed separately. The increase when compared with the A:O distribution in all the other cell types taken together is statistically significant (Table III). The A and O groups were compared because of the findings of Aird *et al.* (1953). If the B and AB cases are taken into consideration the result becomes not significant. It has to be taken into account when considering the significance of the A:O finding that the cytological classification of oat and oval cells as separate from the undifferentiated group was made because they looked abnormal in respect of their A and O distribution. Taking account of this by testing the heterogeneity between the five histological groups for A and O only, the difference becomes not significant.

The distribution of the rhesus blood groups, using anti-D only, shows a significant decrease in Rh negatives among the 555 cancer patients (12.43%) as compared with the controls (18.4%). $\chi^2=9.33$ with 1 d.f., $P<0.005$. The deficiency in Rh-negative cases appears to be related to the squamous-cell carcinomata (8.76% of 251 cases, compared with 15.46% of the other 304 cases), $\chi^2=5.66$ with 1 d.f.; but the figures are only doubtfully significant statistically (Table IV).

TABLE IV.—*Analysis of Differences in Relative Proportions of Rhesus-negatives in the Different Histological Types for Cancer Cases and Controls*

| Histological Type | Cancer Cases | | Controls | | Percentage of Rhesus-negatives | | | $\chi^2$ |
|---|---|---|---|---|---|---|---|---|
| | Rh+ | Rh− | Rh+ | Rh− | Cancer | Controls | Diff. | |
| Squamous cell .. | 229 | 22 | | | 8·76 | | 9·64 | 13·54 |
| Oat cell | 119 | 23 | | | 16·20 | | 2·20 | 0·41 |
| Undifferentiated | 84 | 15 | 816 | 184 | 15·15 | 18·40 | 3·25 | 0·64 |
| Adenocarcinoma | 28 | 4 | | | 12·50 | | 5·90 | 0·72 |
| Mixed .. | 26 | 5 | | | 16·13 | | 2·27 | 0·10 |
| Total .. | 486 | 69 | 816 | 184 | 12·43 | 18·40 | 5·97 | 9·33 |

*Analysis*

| | D. of F. | |
|---|---|---|
| Sum of $\chi^2$ for the different histological types .. | 5 | 15·41 |
| $\chi^2$ for total .. .. .. .. .. | 1 | 9·33 |
| Difference due to heterogeneity .. .. .. | 4 | 6·08 |

This analysis provides no evidence of any heterogeneity.

The comparison of squamous cell with other cases referred to in the text is again picking out an extreme value and comparing it with the others, and cannot be regarded as conclusive, although the possibility of a real difference in the squamous-cell type should not be entirely dismissed.

TABLE V.—*Analysis of Differences in Relative Proportions of Rhesus-negatives in the Different ABO Groups for Cancer Cases and Controls*

| Blood Group | Cancer Cases | | Controls | | Percentage of Rhesus-negatives | | | $\chi^2$ |
|---|---|---|---|---|---|---|---|---|
| | Rh+ | Rh− | Rh+ | Rh− | Cancer | Controls | Diff. | |
| A | 197 | 29 | 329 | 77 | 12·83 | 18·97 | 6·14 | 3·91 |
| B | 36 | 2 | 69 | 12 | 10·34 | 16·81 | 6·47 | 1·29 |
| AB | 16 | 4 | 25 | 7 | | | | |
| O | 237 | 34 | 393 | 88 | 12·55 | 18·30 | 5·75 | 4·22 |
| Total | 486 | 69 | 816 | 184 | 12·43 | 18·40 | 5·97 | 9·33 |

This table provides no evidence of any heterogeneity.

It is to be expected that the rhesus groups will be independent of the ABO blood groups, and an analysis of the controls shows this to be so (Table V).

## Discussion

The principal finding of this local survey of lung cancer agrees with that of Aird *et al.* (1954) for the whole country—namely, that the distribution of the ABO blood groups in the cancer cases is normal.

The significance of the increase of group A at the expense of group O in oat-cell carcinoma in our series is debatable, as it is doubtful how far it is justifiable to analyse the

oat-cell tumours separately from other undifferentiated types. Barnard (1943) believed that all these lung carcinomata probably arose from a common parent cell, and the Council for the International Organizations of Medical Sciences (1953) recommended that large, small, and oat-cell tumours should be put together in an anaplastic group. McDonald *et al.* (1951), on the other hand, when re-examining the sections of all the lung cancers seen at the Mayo Clinic between 1906 and 1948, concluded that what they call the bronchogenic small-cell carcinoma was a definite entity pathologically and clinically and should not be included in the general group of undifferentiated cancers. Foot (1952) also separates these small oat-cell tumours from the pleomorphic type. Björk (1947) regarded them as undifferentiated adenocarcinomata but classified them separately, and they made up 24% of his series from the Brompton Hospital. The evidence, therefore, for the oat-cell carcinoma being a distinct variant is conflicting, but we feel that there is enough to justify analysing them separately, particularly as in our series they were nearly all reported on by one pathologist. Graham (1954), although he would not agree with the details of our classification, thinks that some varieties of lung cancer differ from others so much that they should be regarded as distinct diseases with different aetiological factors. Both he and Doll (personal communication) think that squamous carcinomata are most closely related to cigarette smoking, and it may be that the oat-cell tumour has different causes, possibly with an inherited factor associated with the A blood group.

It would appear from the results of this investigation that rhesus-negative people are slightly less likely to develop lung cancer than those who are rhesus-positive. Aird *et al.* (1954), on the other hand, found 16.2% of rhesus-negative cases among 635 lung-cancer patients, a figure which is within normal limits for the general population of England. We therefore feel that no definite conclusion can be drawn from our figures, but it would be worth while seeing how far a significance could be maintained in a larger series taken over a longer period from the same source.

### Summary and Conclusion

The blood groups of 777 histologically proved cases of carcinoma of lung in one hospital are compared with those of 1,000 blood donors in the same area. No significant or near-significant difference is found in the ABO distribution of the two series.

On breakdown into histological subdivisions an excess of group A at the expense of group O is found in the oat-cell tumours but not in the other types which have a normal ABO distribution. The significance of this is discussed.

In 555 cases tested with anti-D serum, 12.43% were rhesus negative; when compared with the control figure of 18.4% rhesus-negative this is statistically significant. The deficiency of rhesus-negatives applied particularly to the 251 squamous-cell carcinomata (8.76%). This finding is discussed.

We wish to thank the consultant surgeons and pathologists of the Liverpool Thoracic Surgical Unit for access to their case records and reports. We are grateful to Dr. P. M. Sheppard and Dr. R. Winston Evans for much help and advice in the preparation of this paper, and to Dr. D. Lehane, Medical Director, Liverpool Regional Blood Transfusion Service, for the control figures.

ADDENDUM.—Since this paper was prepared an additional series of 1,030 donors has been received from the Liverpool Regional Blood Transfusion Service. The percentage of Rh-negatives in the controls is now 17.93% of 2,030. Although this is slightly lower than the figure used in the analyses, it makes no material difference to the significance of the results. The ABO distribution of the control series has not been affected by the addition of these new donors.

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# KINKING, ROTATION, AND TWISTING OF THE STOMACH

## WITH SPECIAL REFERENCE TO CASCADE STOMACH AND CHRONIC GASTRIC VOLVULUS

BY

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AND

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In routine *x*-ray work the stomach is sometimes seen to be kinked upon itself (as in the "cascade" form), or rotated in its entirety (the more obvious variety of volvulus), or twisted like a cloth being wrung dry (torsion of the stomach). It is convenient to consider these conditions together, because they are often seen with one another in the same patient and sometimes cause similar symptoms. Epigastric distension may lead to diagnostic difficulty, and pain may mimic that of cardiac ischaemia. This paper is an attempt to introduce some unity of concept into the study of these deformities and the clinical pictures which may go with them.

### Anatomical Features

#### Kinking

This term may be used when there is angulation of the gastric wall at any other situation than that of the natural incisura angularis.

*Cascade Stomach* ("*Cup-and-spill*" *Stomach*).—In this condition the gas-filled fundus falls backwards, when the subject is erect, out of the main gastric axis, forming a separate pocket (Fig. 1). The gullet usually enters the medial aspect of this pocket, and swallowed fluid pools in it until the level rises high enough for a "cascade" to take place into the body of the stomach; *x*-ray illustrations are shown in Figs. 8 and 9. Since Rieder first described the condition in 1910 very many cascade stomachs must have come to operation, when they had usually already been aspirated, or to necropsy, when they were flaccid: no exact description is available of their anatomical features. Barclay (1933) was inclined, quoting Forsell, to attach some importance to the sling of oblique fibres which encircles the greater curvature; other

FIG. 1

theories of causation are discussed by Roussel (1952). Regelsberger, quoted by Myles (1937), estimated the frequency of cascade stomach at 3%. In our own last 200 opaque meal examinations, in which we have been looking for it specially, it has been encountered 7 times.

*Jack-knife Stomach* ("*Hinge Volvulus*").—Sometimes a cascade stomach is acutely kinked on itself, the angle pointing upwards and usually forwards. A selected view, typically the right anterior oblique, then shows (Figs. 2 and 10) what has been well described as a "jack-knife stomach" (Cardon *et al.*, 1947).

FIG. 8.—Case 1: cascade or cup-and-spill stomach.

FIG. 9.—Case 2: cascade stomach, right lateral view.

**Rotation**

The natural stomach is fixed, or almost so, at the cardia and the pylorus. In ordinary circumstances the ligaments and vessels allow rotation through some 90 degrees round its long axis, but abnormal mobility may be permitted by slackness or rupture of these structures. Dr. Henry T. Howat and Professor Robert Platt have shown one of us films of an interesting case in which rotation occurred after splenectomy; presumably it was a consequence of operative interference with the gastro-splenic omentum and the vasa brevia. Published reports suggest that a large diaphragmatic hernia (Weeder, 1935), "eventration of the diaphragm" (Deloyers and van der Stricht, 1949), hour-glass stomach (Deaver and Ashhurst, 1921), or carcinoma of the stomach (v. Haberer, 1912) may predispose to abnormal gastric rotation. The possible influence of a distended colon is discussed later.

FIG. 2

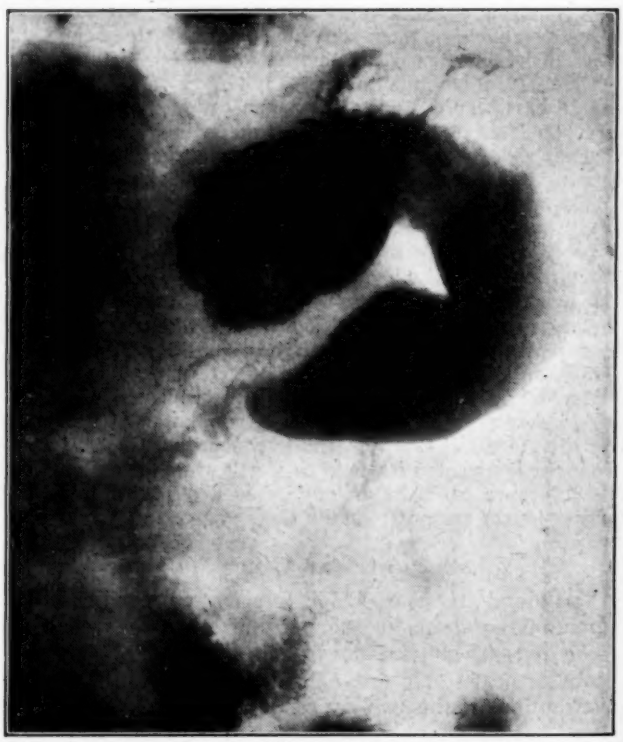

FIG. 10.—Case 3: jack-knife stomach, right lateral view with patient erect.

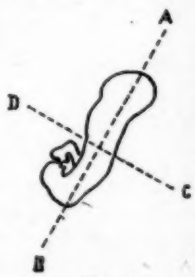


FIG. 3

It is possible for a body free in space to rotate round three different axes and combinations of these. The two main axes in the case of the stomach are shown in Fig. 3: one the long axis of the organ (AB), the other at right angles to it, but also approximately in the coronal plane (CD). The third axis, perpendicular to the page, is not shown. The two pure forms of complete gastric rotation are the longitudinal and the transverse.

*Longitudinal.*—In this form, called by Kocher in 1914 "*organo-axial volvulus,*" the whole stomach rotates round the axis AB. Commonly, the greater curvature moves forwards, then upwards and to the right, then backwards. Rarely (Neumann, 1906; Gharpure, 1939; Whitwell, 1952), it may be displaced first backwards, then upwards and to the right, then forwards. In either case, if the rotation stops at 180 degrees the greater curvature forms the upper border of the stomach. It is a useful distinction from extreme cascade stomach without rotation that in longitudinal rotation through 180 degrees the pyloric antrum must point downwards (Figs. 4 and 11). Films may show spiral twisting of rugal folds at cardia

FIG. 4

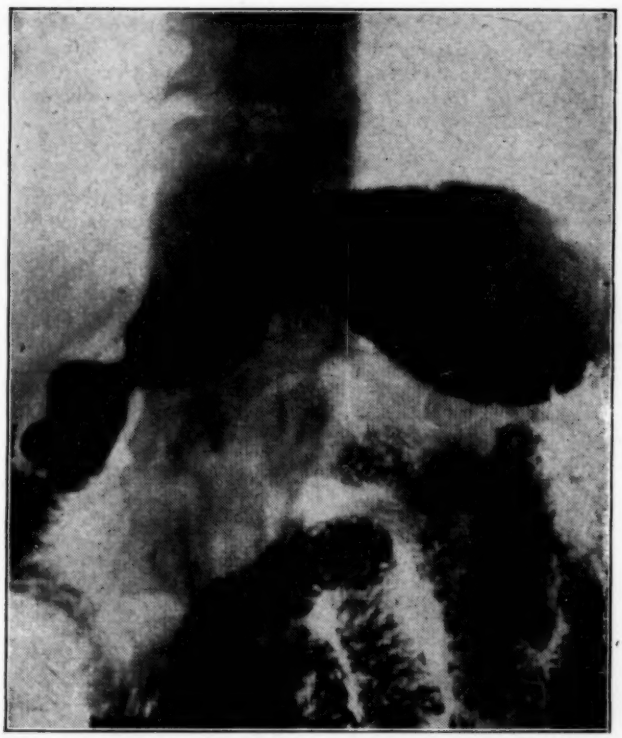

FIG. 11.—Case 4: longitudinal rotation through 180 degrees with patient erect.

or pylorus. And the transverse colon may be carried upwards with the greater curvature to a position above the stomach.

*Transverse* ("*Mesentero-axial Volvulus*").—Here the stomach rotates round the axis CD. So far as is known, this occurs in one direction only—clockwise when one looks from the stomach towards the liver. The pyloric antrum becomes stretched and elongated, so that it ends up crossing the front of the gullet (Figs. 5 and 12).

FIG. 5

Commoner than either of the pure forms of total gastric rotation is a mixed type, which may be regarded as rotation round axes AB and CD simultaneously, or round an axis intermediate between the two, and although pure rotation round the third (antero-posterior) gastric axis is unknown—it would mean, if it were through 180 degrees, ex-

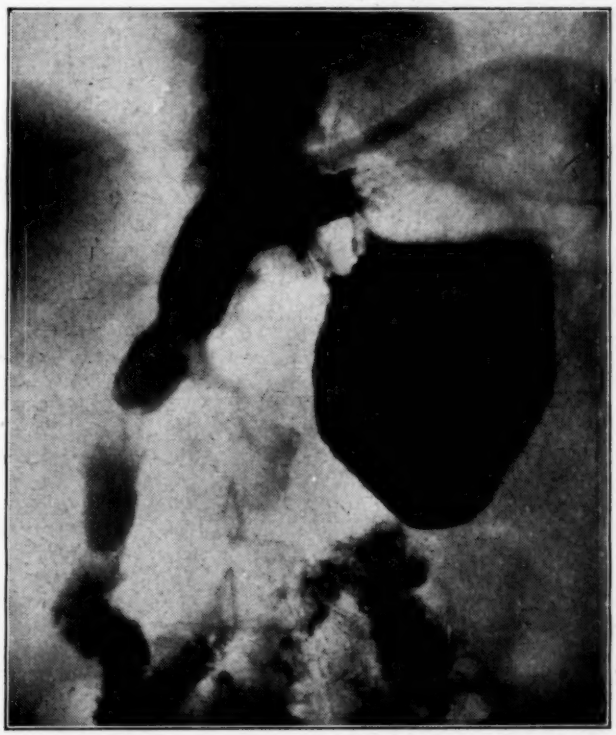

FIG. 12.—Case 5: transverse rotation through 180 degrees.

change of positions between cardia and pylorus—in occasional cases there is an element of rotation also round this axis, as those of Weiss (1923) and Meisels (1925), in which the pylorus was displaced well to the left of the midline.

FIG. 6

**Twisting**

Twisting is best demonstrated in mucosal films, when the spiral arrangement of the rugae is seen. If the folds on the front and back

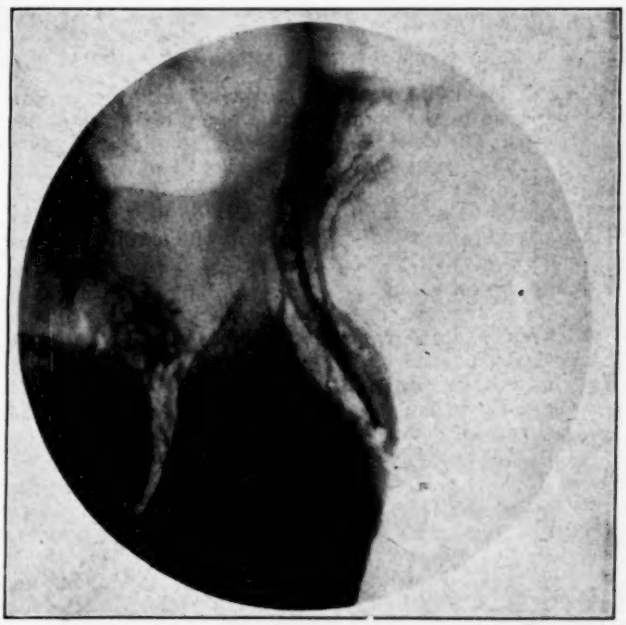

FIG. 13.—Case 6: twisting of upper part of stomach.

walls of the body cross one another, either the fundal or the pyloric end of the stomach must lie in an abnormal position. The two resulting deformities are as follows :

*Twisting of the Upper End* (Figs. 6 and 13).—We have seen this only in association with cascade stomach, though the cascade may not be visible at the same moment as the twist. (A very local twisting which may occur in the neighbourhood of a hiatus hernia is not here considered.)

FIG. 7

*Twisting of the Lower End* (Figs. 7 and 14).—This may occur with cascade stomach or independently. The pyloric antrum points downwards, just as when there is longitudinal rotation of the whole stomach.

FIG. 14.—Case 7: twisting of lower part of stomach.

## Reported Clinical Features

Cascade stomach is generally considered to be a symptomless variation of the normal form. Many of the cases one sees support this view, but the writings of Continental authors (Roussel, 1952) suggest that in a number of cases there may be complaints. The main ones are thought to be epigastric discomfort and distension, and when there is "jack-knife" accentuation pain may cause confusion with coronary disease (Cardon *et al.*, 1947).

Acute gastric volvulus, first reported by Berti (1866), is one of the rare causes of an abdominal emergency. Dalgaard (1952) reviewed 150 cases. The clinical picture is one of abdominal pain and circulatory collapse, with the triad of features described by Borchardt (1904)—ineffective retching, epigastric distension, and failure of a tube to pass the cardia, at least without difficulty.

Less acute or severe cases of volvulus, diagnosed in the *x*-ray room, have not attracted such attention. The first was that of Desternes and Baudon (1912). Hamilton (1945) has reported the largest series—11 cases. Other accounts are those of Rosselet (1920), Rosselet and Gilbert (1922), Choisy and Babaiantz (1927), Sutter (1928), Caillods and Cottet (1929), Ranzi (1930), Azmy and Marey (1932), Löw-Beer (1932), Myles (1937), Singleton (1940)—with a helpful review—Silverstein (1947), Cardon *et al.* (1947), and Brohée *et al.* (1949). Some of the patients had attacks of epigastric distension, discomfort, or pain, and the site and radiation of the pain have caused confusion with cardiac ischaemia.

## Method of Inquiry

We have selected cases with grossly kinked, rotated, or twisted stomachs from the written records of 8,000 opaque meal examinations between 1924 and 1952, and investigated their features from the films of the stomach and colon (follow-through was usual) and from the clinical records.

It was desired to review for comparison a control series of patients without kinking, rotation, or twisting of the stomach. As most of the patients at this hospital have opaque meal examinations, and only a small proportion have gastric disease, it has been thought reasonable to consider as the control for each patient with an abnormal stomach form the next patient to have an opaque meal. One of us looked out the cases, and the other made the analysis of clinical features from the mixed records.

A number of other patients with abnormal stomach forms have been seen or heard of, often through the kindness of physicians, surgeons, and pathologists elsewhere. What has been learnt from them has been drawn on freely for the purposes of this paper, but no extraneous cases are included in the numerical analysis.

## Classification of Cases

Forty-four cases with kinking, rotation, or twisting of the stomach have been classified radiologically according to the definitions given above. Many appear under more than one heading, as shown below. Decision about individual cases has not always been easy, and even when a number of films of good quality are available at different stages of filling and from different angles there may be doubt about the nature of a deformity. No distinction is made between a case presenting more than one abnormality at a single examination, or different abnormalities at each of two or more examinations. In some of our subjects the deformity has been chronic, in others intermittent.

*Cascade Stomach*

| | | |
|---|---|---|
| Uncomplicated | 12 | |
| With jack-knife stomach (not distinguished from cascade stomach in lower parts of the table) | 7 | |
| With twisting of upper part only | 5 | 30 |
| With twisting of lower part only | 4 | |
| With, at different times, twisting of both upper and lower parts and longitudinal rotation | 1 | |
| With mixed longitudinal and transverse rotation | 1 | |

(In 1 case the fundus was posterior and medial, in 17 cases directly posterior, in 9 cases posterior and lateral, and in 3 cases lateral.)

*Longitudinal Rotation*

| | | |
|---|---|---|
| Uncomplicated | 3 | |
| Mixed with transverse rotation (1 with cascade stomach) | 9 | 13 |
| With at different times cascade stomach and twisting of both upper and lower parts | 1 | |

*Transverse Rotation*

| | | |
|---|---|---|
| Uncomplicated | 1 | 10 |
| Mixed with longitudinal rotation (1 with cascade stomach) | 9 | |

*Twisting of Upper Part*

| | | |
|---|---|---|
| Uncomplicated | 0 | 6 |
| With cascade stomach (1 with, on different occasions, longitudinal rotation and twisting of lower part) | 6 | |

*Twisting of Lower Part*

| | | |
|---|---|---|
| Uncomplicated | 2 | 7 |
| With cascade stomach (1 with, on different occasions, longitudinal rotation and twisting of upper part) | 5 | |

## Illustrative Cases

*Case 1* (*Fig. 8*).—Cascade or cup-and-spill stomach, with abnormally large air-bubble. A diabetic man of 46, who passed an excessive amount of flatus, but otherwise had no relevant symptoms.

*Case 2* (*Fig. 9*).—Cascade stomach, right lateral view. The form of this stomach was substantially unchanged by air inflation of the colon, and by subsequent passage of intestinal contents following subcutaneous injection of vasopressin ; this film was taken shortly after complete evacuation of the colon. The patient was a woman of 50 with idiopathic steatorrhoea. She had attacks of irritability and

abdominal discomfort, when she was observed to swallow air copiously, to belch it a little, and to develop swelling and superresonance in the left upper quadrant of the abdomen. Colonic air inflation gave rise to the same symptoms and signs.

*Case 3* (*Fig. 10*).—Jack-knife stomach, right lateral view with patient erect. A man of 51, with an irritable colon. He was many times observed in attacks of abdominal distension, and gave an account of having burst a wound after appendicectomy.

*Case 4* (*Fig. 11*).—Longitudinal rotation through 180 degrees. Patient erect, as may be seen from the small air-bubble in the middle of the stomach. The pylorus points downwards. The transverse colon was above the stomach, at the level of the twelfth thoracic vertebra. The patient was a man of 50 who had some abdominal complaints and mentioned distension; the psychoneurotic nature of his illness made these symptoms difficult to evaluate.

*Case 5* (*Fig. 12*).—A housewife of 48 was playing bridge when she was seized with a sudden pain across the front of the chest, with radiation to the neck, both jaws, and the fingers of both hands. It went away while she continued the game, but two days later she had a similar attack and was admitted to hospital. On this and later occasions electrocardiograms taken between attacks showed no abnormality. Other attacks, often with abdominal distension and palpitation, were thought to be relieved by glyceryl trinitrate, but as no attack was ever prolonged this effect could not be established. Two years after the first attack a laparotomy was made and the stomach was found in an abnormal position. It was anchored by stitches, as it was thought, where it should have been, but *x*-ray films taken when she came to this hospital five years later showed transverse rotation through 180 degrees. Note the drawn-out and downward-pointing pyloric antrum.

*Case 6* (*Fig. 13*).—Twisting of mucosal folds in the body of the stomach. The pyloric end of the stomach is in normal position. The direction of the twist is shown in other films by the demonstration that the oesophagus crosses the front of the fundus to reach the cardia. Other examinations from 1926 to 1952 showed sometimes a cascade form, sometimes jack-knife kinking, sometimes twisting of the pyloric end, and once probably longitudinal rotation; the air-bubble was sometimes very large. The patient, a man of 52, had at one time an ulcer high on the lesser curvature; he mentioned abdominal distension and discomfort in the right side of the abdomen.

*Case 7* (*Fig. 14*).—Twisting of the pyloric end of the stomach. Note crossing mucosal folds in the body of the stomach, and downward-pointing pyloric antrum. The transverse colon was just above the pyloric end of the stomach, at the level of the first lumbar vertebra. The patient was a woman of 55 who had had a cholecystectomy five years before and then two operations for adhesions. Her symptoms were probably not relevant to the gastric deformity.

## Analysis, with Comments

The following significant differences were found between patients with these abnormal forms of stomach and the controls:

*Sex Distribution.*—The patients with abnormal stomach forms were 32 men and 12 women; the controls were 26 men and 18 women. The higher proportion of men in the first group derives from the uniform male sex of the 13 patients with longitudinal rotation (including the 10 patients with other abnormality of form in addition). The odds against this uniformity of sex happening by chance are more than 50 to 1 ($P<0.02$).

*Adhesions.*—Operative or *x*-ray evidence of adhesions was recorded in seven of the patients with abnormal stomach forms and in two of the controls; this difference is not statistically significant, but of seven patients with jack-knife stomach three gave evidence of adhesions ($P<0.02$).

*Really Severe Distension.*—Eight of the 44 patients with abnormal stomach forms had either been observed in really severe attacks of abdominal distension or gave stories of them, compared with only 1 of the 44 controls, a man with gall-stones ($P<0.05$). These eight cases were distributed between all the main groups in our classification. Two patients with jack-knife stomach gave a history of abdominal wounds having burst after operations, and a patient with longitudinal rotation has since had the same surgical accident. In another patient with twisting of the lower stomach the girth of the abdomen increased 5 in. (12.5 cm.) during an attack. There was repeated mention of tympanites and splashing in the records.

*Gastric Air-bubble.*—An abnormally large air-bubble was present in 19 of the patients with abnormal stomach forms and in two of the controls ($P<0.01$).

*Left Dome of the Diaphragm Higher than Right.*—This was observed in nine of the patients with abnormal stomach forms, and in one of the controls ($P<0.02$).

*High Left Colic Flexure.*—Present in 26 of the patients with abnormal stomach forms and in 10 of the controls ($P<0.01$).

*Distended Left Colic Flexure.*—Present in 10 of the patients with abnormal stomach forms and in two of the controls ($P<0.05$).

*Abnormally High Transverse Colon.*—The mid-transverse colon was at the level of the eleventh and twelfth thoracic vertebrae in the two cases of pure longitudinal rotation in which the stomach was in the abdomen. In none of 36 controls in which the level could accurately be determined did it rise so high ($P<0.01$).

Certain further features were noted in the cases with abnormal stomach forms, though a statistical correlation was not established:

In two patients *past surgery* seemed to have been responsible for the gastric deformity.

In one patient *gastric carcinoma* was perhaps responsible for the deformity.

*Massive diaphragmatic hernia* was a feature in two of the abnormal cases.

In two patients, one with a jack-knife stomach and one with transverse rotation, there was *retrosternal pain radiating down the arms* with no relation to exertion; electrocardiograms were normal between attacks. This occurred in three other cases of gastric rotation which are not in the present series.

*Regurgitation, vomiting, and belching* were all rather more frequent in the abnormal group than among the controls.

A number of other possible associations investigated were not found to differ in the two groups: mean age and weight (allowing for sex) were similar, and various categories of abdominal disorder occurred with comparable frequency.

In 9 of the 44 patients with cascade stomach or volvulus the main symptoms for which they sought relief appear to us to have been associated with the gastric deformity. In only one case did the deformity influence a decision about treatment in favour of gastric surgery.

## Discussion

Evidence has been produced that there is an association between certain abnormal stomach forms and both gastric pneumatosis and a high distended left colic flexure. Gas in the stomach and in the intestine is largely ingested air (Maddock *et al.*, 1949); but the available facts do not settle whether in our cases air-swallowing or gastric deformity or an abnormal colon was the primary factor. We have seen cases in which psychoneurotic air-swallowing seemed to be the main feature, and the shape and position of the stomach might well be altered by such a habit; on the other hand, the discomfort associated with an abnormal stomach may aggravate the tendency to swallow air. It is recognized that the left half of the transverse colon can produce a filling defect in the greater curvature or even a "bilocular stomach," but the deformities considered in this paper are rather different. In two recent patients, one with cascade stomach and the other with a mixed type of rotation, films of the stomach were taken after colonic air inflation, and again when the colon had been emptied after subcutaneous injection of vasopressin ("pitressin"); in neither case was deformity much affected.

The most common clinical feature in our cases has been epigastric distension due to gastric and colonic pneumatosis. Ramond (1927) did not write specially about abnormal gastric forms, and indeed he believed that the cascade appearance was secondary to distension, but he emphasized

that patients might be distressed by a large gastric air-bubble. He thought an aggravating feature might be failure of the cardia to relax and allow belching, an *aérophagie bloquée* being more troublesome than an *aérophagie libre*. The condition he described as *aérophagie* included *aérogastrie* and *aérocolie*, for he pointed out that most swallowed air which is not belched back must pass on into the lower bowel. His attractive and logical writings used to be quoted by Hurst, who described imprisonment of the gastric air-bubble in oesophageal ulcer (Hurst, 1934) (incidentally, the published films of his main case show a cascade stomach), and believed that "wind round the heart" also occurred (Hurst, 1938, 1942) if the gastric cardia was dislocated by an excess of gas in the left colic flexure; then the vicious circle might be broken by an injection of vasopressin.

Sometimes, both in cases in the literature and in others we have come across ourselves, epigastric or low chest pain has radiated to the neck, jaws, arms, and hands. The mimicry of ischaemic heart pain is striking and misleading, though a recurrent tendency may exclude coronary occlusion, while there is not the constant relation to exertion which one expects in angina of effort. Similar radiation of pain is sometimes seen in hiatus hernia and high lesser-curve gastric ulcer. It is hardly surprising, for there are communications between the sympathetic nerve supplies to heart and gullet (Kuntz, 1946). It is also possible, as Roemheld (1931) suggested might happen in his "gastro-cardiac syndrome," that the heart is embarrassed by upper abdominal distension. It is interesting that Dworken *et al.* (1952) should describe pain like that of cardiac ischaemia in their "splenic flexure syndrome."

It is usually unnecessary to mention the abnormal form of stomach to these patients, and most of them require no treatment. If abdominal distension is troublesome they should be advised against gulping food or drink, and it should be explained that unconscious air-swallowing often accompanies attempts to belch. It may be helpful for them to avoid greens, and to take a level teaspoonful of charcoal three times daily after food. We have not yet used vasopressin regularly in any case. We have instructed one patient (not in this series) in the use of a fine stomach-tube, after showing him the relief it could give, but he did not carry on with it: it is stated that in some cases with severe rotation a fine stomach-tube, or even a large one, cannot be passed. More troublesome recurrent attacks may rarely justify surgery, such as partial gastrectomy or gastropexy (either simple or by means of gastrostomy with later closure); Anagnostidis (1935) has reviewed the operations for gastric volvulus done up to the time of his report. The treatment of acute gastric volvulus is usually surgical, with parenteral replacement of fluid and electrolytes. But cascade stomach and gastric rotation and twisting are usually unimportant incidental findings, and the greatest harm they are in most cases likely to do is to interest a physician or surgeon who does not recognize this fact.

When laparotomy is considered for any reason in a patient with one of these deformities the risk of severe post-operative distension should be borne in mind: 3 out of 44 patients in this series had burst abdomens before or after they were here.

### Summary and Conclusions

Kinking, rotation, and twisting of the stomach are usually incidental *x*-ray findings. There is, however, an association with pneumatosis of the stomach and of the left colic flexure. Patients may complain of discomfort and distension in the upper abdomen, and there is a risk of burst abdomen after laparotomy. Pain may occur with similar radiation to that seen in cardiac ischaemia.

We are indebted to Dr. F. Avery Jones, who stimulated this study and helped with its presentation; and to past and present physicians at Ruthin Castle, whose records form the basis of the work.

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# DIAGNOSIS AND RESULTS OF TREATMENT OF CANCER OF THE PANCREAS AND AMPULLA OF VATER

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In spite of many statements to the contrary (Robson and Moynihan, 1902), there is a widespread impression that carcinoma of the pancreas produces painless progressive jaundice. The case histories of 190 patients have been studied, the majority of whom have been under the care of one or other of us, the remainder being under the care of colleagues at St. George's or St. Mary's Hospitals. As a result of this study we have come to the conclusion that most of the standard textbook descriptions of this disease are incorrect. In this paper we discuss the symptoms and signs of carcinoma of the pancreas in an effort to make the diagnosis easier, and we present the results of treatment, which show that diagnosis at an operable stage has been of value.

### Diagnosis

Carcinoma of the pancreas is a disease of middle and later life; in our series the youngest patient was aged 43 and the oldest 89. The majority of cases occurred in patients between 50 and 70 years of age. Table I gives the anatomical situation of the primary tumour within the pancreas. It will be seen that in 128 patients (67.3%) the carcinoma arose in the head of the pancreas or in the ampulla of Vater; in 51 patients (26.8%) it was placed in the tail and

body, or involved the whole gland; 8 patients (4.2%) presented with a carcinoma of the common bile duct—all of these suffered from gall-stones as well; and in two patients the primary tumour was considered to be a sarcoma and in one a cystadenocarcinoma.

TABLE I.—*Site of Primary Tumour in* 190 *Patients with Cancer of Pancreas or Distal Bile Duct*

| | |
|---|---|
| Head of pancreas or ampulla of Vater | 128 |
| Common bile duct | 8 |
| Body and tail or the whole gland | 51 |
| Sarcoma | 2 |
| Cystadenocarcinoma | 1 |

In this table a distinction has not been made between growths of the head of the pancreas proper and ampullary growths. It is recognized that such a distinction should be made where possible, on both diagnostic and therapeutic grounds, but the records of some of the earlier patients in the series did not describe the exact origin of the tumour with this particular distinction in mind. The 128 patients therefore include some undoubted tumours of true pancreatic origin and some in which the site of origin was uncertain. References later to points of difference between ampullary and pancreatic tumours are based upon those cases only in which the type of tumour was considered to be established.

## Symptoms

Table II lists the first symptom in 184 of the 190 patients under review. The outstanding points in this table are that pain was the first complaint in 108 (58.7%) patients, that no patient with carcinoma of the body or tail of the gland became jaundiced until late in the course of the disease, and, above all, that in patients with carcinoma of the head

TABLE II.—*The First Symptom*

| | Pain | Jaundice | Others |
|---|---|---|---|
| Carcinoma of head of pancreas or ampulla of Vater | 59 | 54 | 14 |
| Carcinoma of body or tail | 49 | 0 | 8 |

of the pancreas or the ampulla of Vater pain was the first symptom on more occasions than jaundice. This latter point is a direct contradiction of the clinical picture given in most textbooks, where the supposed absence of pain in the early stages of this disease is stressed. That there is nothing new about this fact becomes obvious when one quotes from the writings of Robson and Moynihan (1902): "The earlier symptoms almost invariably refer to the digestive organs. . . . Pain in the epigastrium radiating round one or both sides of the back is sometimes excessive, wearing, almost intolerable. . . . In one-half of cases at least, the suffering is exquisite and is not infrequently worse at night."

The pain in the early stages of cancer of the pancreas takes two forms. Patients with a tumour in the head of the gland complain of a dull ache or discomfort in the epigastrium; occasionally it resembles biliary colic, but more often the upper alimentary tract is suspect and the patient is treated with an alkaline powder. On the other hand, patients with a tumour of the body or tail of the gland complain of pain in the epigastrium which radiates round to the back. This pain has a characteristic feature of considerable diagnostic value: it is worse when the patient lies down and better when standing or sitting up: as a result it is more severe at night; often these patients sleep sitting up.

Jaundice caused by pancreatic carcinoma, in addition to altering the colour of the skin, is invariably associated with pale stools and dark urine. Again, our findings have been the opposite to those in most of the textbooks: the jaundice is not necessarily progressive; in most patients with carcinoma of the ampulla of Vater and a few with a tumour of the head of the pancreas the degree of jaundice has fluctuated. Indeed, in one patient the jaundice completely cleared, yet exploration for a suspected gall-stone in the common bile duct revealed an ampullary carcinoma.

Pain and jaundice, considered together, may provide some evidence, though not conclusive, on which to base a distinction between ampullary and true pancreatic carcinomas, for, as might be expected, evidence does suggest that jaundice is more likely to precede pain in an ampullary than in a pancreatic tumour.

Twenty-two patients gave as their first symptom something other than pain or jaundice. The majority of these complained of vomiting. In some this was so severe that pyloric stenosis was diagnosed. These patients with severe vomiting had in every case a carcinomatous obstruction due to invasion of the stomach or duodenum. If the duodenal involvement was distal to the entrance of the common bile duct the vomit contained bile and pyloric stenosis could be excluded. In the others, even a barium meal failed on occasion to give the correct diagnosis.

Invasion of the duodenum does not necessarily indicate a bad prognosis, because the portal vein is sometimes free from growth and resection is possible after adequate preoperative preparation. The remainder of these 22 patients presented with symptoms of an entirely different nature: one patient who had an ampullary carcinoma presented as a case of severe anaemia due to bleeding into her alimentary tract; her haemoglobin on admission was 30% (4.5 g.). And in two patients the first symptom was caused by a metastasis: one had an enlarged cervical lymph node and the other an enlarged femoral lymph node which was thought at first to be an irreducible femoral hernia.

Apart from the first symptom, patients with pancreatic tumours soon develop other clinical abnormalities. Table III lists the frequency of the main symptoms in the patients of this series. As will be seen, jaundice developed before death in every patient with an ampullary carcinoma, in 94% of those with a carcinoma of the head of the pancreas, but in less than 5% of those with a tumour of the body or tail of the gland. Loss of weight was a prominent feature, often appearing fairly early in the course of the disease. Diarrhoea and vomiting were both frequent symptoms, but all 16 patients who complained of a palpable mass were inoperable by the time they reached the surgeon.

TABLE III.—*Frequency of Main Symptoms*

| Symptoms | No. of patients | Comment |
|---|---|---|
| Pain | 131 | Present in 50% of ampullary carcinoma, 90% of carcinoma of head, and 100% with carcinoma of body or tail |
| Jaundice | 128 | Present in every case of ampullary carcinoma and 94% with carcinoma of head of pancreas |
| Loss of weight | 165 | |
| Lassitude and anorexia | 84 | |
| Diarrhoea | 61 | |
| Itching | 58 | |
| Vomiting | 43 | |
| Tumour noticed by patient | 16 | |
| Palpable lymph nodes | 9 | |

Clinical examination of these patients may show widespread abnormalities due to jaundice, liver failure, or metastases; but in the diagnosis of pancreatic carcinoma abdominal inspection and palpation have been a valuable source of abnormal physical signs. Table IV gives some of the

TABLE IV.—*Abdominal Palpation*

| | | | |
|---|---|---|---|
| Palpable gall-bladder | 72 | Ampullary carcinoma | 46% |
| | | Carcinoma of the head | 58% |
| Palpable tumour | 37 | Carcinoma of the head | 2·5% |
| | | Carcinoma of the body or tail | 60% |

information obtained from this examination. It is of interest that the gall-bladder was palpable in only 72 patients, or 56% of those who were jaundiced; in nearly every patient the gall-bladder was enlarged, but the liver was enlarged as well, which shielded the gall-bladder from the hand of the clinician. The other interesting fact which emerges from this study is that the tumour was palpable in 60% of patients with carcinoma of the body or tail of

the pancreas, but by this time these tumours are nearly always inoperable and the fact that they are palpable usually means that the diagnosis has been delayed.

### Investigations

*X*-ray and other investigations have been of help in some patients. All those with jaundice showed the characteristic abnormalities of liver function associated with post-hepatic or obstructive jaundice. Occult blood was present in the stools of 11 out of 15 (73%) patients with carcinoma of the ampulla of Vater; this test is of value in these patients. Table V also gives the results of barium-meal examination; in 18 out of 70 patients positive evidence of cancer of the pancreas or ampulla was obtained by this investigation.

TABLE V.—*Results of Investigations*

| | |
|---|---|
| Barium meal | In 18 out of 70 patients positive evidence obtained |
| Occult blood in stools | Positive in 11 out of 15 patients with an ampullary carcinoma |
| Biochemical tests for obstructive jaundice | Positive, whenever done in a jaundiced patient |
| Examination of duodenal aspiration; Examination of stools for unsplit fat or meat fibres | Unreliable |

Radiological evidence of malignant obstruction of the terminal common bile duct may also be obtained by injecting radio-opaque substances directly into the dilated intrahepatic duct system, as shown recently by Nurick, Patey, and Whiteside (1953), and Rodney Smith (1954). This transhepatic cholangiography, under local analgesia, can demonstrate very clearly the dilated common bile duct and the exact site of an obstruction. Moreover, the irregular shape of an obstruction by a carcinoma can be distinguished from the rounded filling defect of an impacted gall-stone. There are, however, disadvantages in the method, the chief of which is the risk of subsequent leakage of bile into the peritoneal cavity. Severe abdominal pain and shock may then call for urgent laparotomy if death from peritonitis is to be avoided.

Having used this method of investigation and studied the results of others, we feel that the evidence obtainable, while of some value, does not outweigh this grave disadvantage. If leakage does occur, not only may the patient lose his life, but even if this is prevented by early laparotomy it may well be found that the peritoneum and cellular planes are sodden with bile and that the general condition of the patient forces the surgeon to be satisfied with a palliative short-circuit instead of attempting resection.

### Comment

The symptoms and clinical signs present in this series of 190 patients indicate that most sufferers from carcinoma of the pancreas are between 50 and 70 years of age and exhibit one of the two main clinical pictures. Unusual cases sometimes occur. The first picture is that seen in patients with carcinoma of the head of the pancreas or ampulla of Vater; in these patients the most frequent symptom is epigastric pain resembling peptic ulceration or cholecystitis, followed after a variable interval by jaundice. The second picture occurs in patients with tumours of the body or tail; they complain of a different type of pain which starts in the epigastrium and passes round one or both sides to the back; this pain is worse when the patient lies down, and better when sitting up or standing. These patients are not jaundiced until later in the course of the disease.

Of the unusual cases the most important are those in which the duodenum is invaded and symptoms similar to those seen in pyloric stenosis are produced. This occurs in about 5% of patients.

### Treatment

Early diagnosis would be only of academic interest if treatment failed to influence the course of the disease. Table VI gives the result of treatment in the patients of this series. It will be seen that the average survival after excision

TABLE VI.—*Results of Treatment*

| Treatment | No. of Patients | Average Survival | |
|---|---|---|---|
| Nothing surgical | 44 | 7 weeks | |
| Exploratory only | 59 | 13 ,, | Including operation deaths |
| Short circuit (cholecyst-gastrostomy, 21; cholecyst-jejunostomy, 44) | 65 | 23 ,, | Including operation deaths |
| Excision | 22 | 17 months | Including operation deaths |

was nearly ten times that of those patients who received no active treatment and three times that of a short-circuit operation. In addition the longest survival after excision has been 5¼ years, whilst, with one exception, no patient has lived for more than 12 months after a short-circuit operation. It appears, therefore, that excision is worth while in selected patients. We feel that radical surgery should be limited to those cases in which the growth is without doubt operable. The operative mortality has been 5 out of 32 (15.6%) patients, and all but three were one-stage procedures (Table VII).

TABLE VII.—*Pancreatic Resection for Cancer: Operative Mortality (Including Several Recent Cases not Included in the 190 Subjected to Clinical Analysis)*

| | Resections | Deaths | Percentage Mortality |
|---|---|---|---|
| Radical pancreato-duodenectomy | 30 | 4 | 13·3 |
| Cystadenocarcinoma of body and tail | 1 | 0 | 0 |
| Sarcoma of body (gastro-colo-pancreatectomy) | 1 | 0 | 0 |
| Total | 32 | 4 | 11·5 |

The main reasons why excision was not carried out in 156 of our cases were: 16 patients had domestic or other reasons—in several the war was responsible; 29 were unfit for major surgery; 58 had widespread metastases; and 53 were considered to be inoperable on account of fixation to the portal vein or some other important structure. We feel very strongly that it is a mistake to attempt the removal of a tumour which is adherent to these structures. Such surgery carries a high mortality and rarely, if ever, does good.

### Summary

The clinical findings of 190 patients with cancer of the pancreas and distal bile duct have been analysed.

The clinical features of this disease resemble the picture painted by Robson and Moynihan in 1902 more closely than that given in most undergraduate textbooks.

The results of treatment in this series indicate that diagnosis and surgical treatment whilst the tumour is still operable has been an advantage.

We wish to thank those of our colleagues who have given us permission to quote from their case histories, and particularly Professor C. A. Pannett, who was one of the pioneers of pancreatic surgery.

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*Food Composition Tables—Minerals and Vitamins, for International Use* has been prepared by CHARLOTTE CHATFIELD for the Food and Agriculture Organization, United Nations. It gives the figures for vitamin A, ascorbic acid, thiamine, riboflavine, niacin, calcium, and iron content of foodstuffs. These are all nutrients of importance to humans and are also among the nutrients in which human diets are often deficient. A bibliography of 539 items is appended to the tables. The publication is No. 11 of the F.A.O. Nutritional Studies series, and may be obtained from Her Majesty's Stationery Office, price 5s.

# ISCHAEMIC LATERAL POPLITEAL NERVE PALSY

BY

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The importance of vascular factors in the production of peripheral nerve affections has been considered by various authors in articles relating both to clinical and to experimental aspects of the problem. Experimental work and the information arising from cases of tourniquet paralysis have led to discussions on the relative parts played by direct neural compression and ischaemia. Thus, Lewis *et al.* (1931) concluded that ischaemia was of prime importance in producing neural symptoms, and that sensory manifestations in an ischaemic limb were not dependent upon direct nerve compression. Richards (1951) discussed tourniquet paralysis in the upper limbs, and concluded that ischaemia and direct nerve pressure both play some part in this type of paralysis.

Discussions on the common clinical problem of foot-drop usually include a reference to the vulnerability of the lateral popliteal nerve both to direct pressure and to indirect effects of pressure upon its blood vessels. Woltman (1929), in reviewing 29 cases of foot-drop, decided that weight loss followed by local compression of the lateral popliteal nerve in crossing the legs played an important part in the production of the lateral popliteal paralysis, suggesting that arteriosclerosis might also be a contributory factor. Garland and Moorhouse (1952) also emphasized the importance of mechanical factors, and confessed themselves at a loss to explain four examples in which the paralysis was said to have developed suddenly whilst walking. Sunderland (1945) stressed the point that the superficial and unprotected position of the nutrient artery to this nerve makes this vessel particularly susceptible to pressure, with the result that an ischaemic neuropathy may develop. In the literature there are, however, few accounts of the occurrence of frank vascular disturbances in association with foot-drop, although Roberts (1948), in an article dealing with experimental ischaemia of the sciatic nerve in dogs, alluded to a patient with bacterial endocarditis who developed a left lateral popliteal nerve palsy, and in whom post-mortem examination revealed thrombosis of the vasa nervorum in the centre of the affected nerve; whilst Mafson (1952), in reviewing a large series of cases of obliterative arthritis, discovered eight cases of lateral popliteal nerve palsy. The cases described below are all examples of foot-drop associated with a definite local vascular affection, and serve to illustrate the special vulnerability of the lateral popliteal nerve to ischaemia.

### Case 1

A woman aged 51 was seen on February 15, 1952. Six weeks earlier she had developed spasms of pain in the right popliteal space, shooting down into the ankle and foot. After four or five days there was a slight swelling of the foot and ankle. A week later still there was numbness of her right toes and of the distal half of her foot. Four weeks after the initial pains her right foot became very floppy, and it was this symptom which troubled her most at the time of examination. Abnormalities were confined to the right leg and comprised slight oedema from the knee, right foot colder than the left, and absence of right foot pulses. Both femoral and the left foot pulses were easily palpable. There was complete loss of power in the peronei and anterior tibial groups; all other muscles were normal. Reflexes were normal. Sensation to pinprick was diminished over the first and second toes only, to a point just proximal to the heads of the metatarsals. All investigations were normal, apart from electrical stimulation and electromyography, which indicated a lower motor neurone lesion in the lateral popliteal group, the anterior tibials being rather more affected than the peronei.

The patient was given a toe-raising spring but no other treatment. The affected muscles began to improve, and by April 24 (about four months after the onset) the peronei were almost normal and there was appreciable power in the dorsiflexors, though sensation was still impaired, the foot still cold, and the posterior tibial pulse not palpable. The improvement has continued, and on March 19, 1953, she had a normal gait and full power in the dorsiflexors of the foot. She still had "pins and needles" in the area of initial sensory loss, and the right foot was still colder than the left.

### Case 2

A woman aged 44, a known case of rheumatic heart disease with mitral stenosis, suddenly developed a moderate aching pain in the right groin on July 19, 1951. Thirty-six hours later she was awakened by a severe cramp-like pain in the right calf. On getting out of bed her right foot was very weak. She massaged her leg, with some comfort, but four hours later she was reawakened by an even worse pain. She noticed now that the leg had "no colour in it," was very weak both below and above the knee, and felt numb and tingling to a point above the knee. On July 21, forty-eight hours after her first pain, she was seen in hospital, when there was evidence of popliteal thrombosis. Neurological signs comprised weakness of all the muscles of the right leg below the knee, absent ankle-jerk, and an impairment of sensation in the leg. Paravertebral lumbar sympathetic block was performed (Mr. S. Rose) and tocopherol acetate, 1 g. daily, tolazoline hydrochloride, 50 mg. t.i.d., and "cyclospasmol," 100 mg. t.i.d., were given. Within six days the movements of the leg were good, and sensation was almost back to normal. By August 11 she was able to return home "fully mobile." She continued well until February 3, 1952, when for forty-eight hours she had "pins and needles" in the right leg from the knee downwards.

On readmission to hospital, examination showed definite weakness of the anterior tibial and lateral popliteal muscles. A week later a new pain in the right calf was accompanied by the signs of popliteal occlusion, including some swelling of the leg. She rapidly developed a frank right foot-drop with impairment of sensation to pin and cotton-wool over the lower part of the leg and dorsum of the foot. A further paravertebral block on March 3 relieved much of her pain, but little improvement was noted in her neurological signs, and so she was referred to the department of neurology, where the positive findings on March 28 were: well-established mitral stenosis; absence of right pulses at and below the knee; slight wasting of right quadriceps with some fibrillation; extreme wasting of right anterior tibial and peroneal muscles with complete loss of power; a little thinning of the calf muscles, but power excellent; right ankle-jerk absent; sensory loss to pin and cotton-wool in the distribution both of the musculocutaneous and anterior tibial nerves.

The further administration of the vasodilator drugs, and the application of the toe-raising spring, enabled the patient to resume walking. When last seen on July 21, 1952, she still had the partial popliteal palsy, but was able to walk with the aid of the foot spring.

### Case 3

A man aged 51, after two years of angina of effort, developed the symptoms and signs of myocardial infarction.

Six days later, whilst in bed, he had a severe pain in the right popliteal space. As the pain diminished he noticed that his right leg was numb and cold below the knee. No pulses could be felt at the ankle. Severe weakness of the dorsiflexors of the foot was noted immediately, but only slight affection of the posterior tibial muscles. Anticoagulant therapy was given, but at the end of five weeks, when he began to walk about, the degree of foot-drop was severe, and was accompanied both by pain in the calf and by oedema of the foot and leg. This led to his examination in the neurological department on January 15, 1952. Positive findings were: obvious thickening and sclerosis of peripheral vessels, but peripheral pulses palpable; slight oedema of right foot and ankle; considerable wasting of the right anterior tibial and peroneal muscles with complete loss of power in the anterior tibial and severe loss in the peronei; posterior tibial group good power with a little wasting; right ankle-jerk absent. There was loss of sensation to pinprick and cotton-wool over the lower and anterior part of the leg and the dorsum of the foot. Electromyography and electrical stimulation revealed a lower motor neurone lesion in the group of muscles supplied by the lateral popliteal nerve.

During his stay in hospital his muscle power improved a little, but shortly after discharge a further coronary attack proved fatal.

### Case 4

A woman aged 58, who had complained of angina of effort relieved by glyceryl trinitrate for about four years, developed leucoplakia, for which vulvectomy was carried out. Some five weeks after the operation, and shortly before being discharged, she developed a sudden cramp in the left foot, spreading up the back of the leg as far as the knee. This pain continued for two weeks, and she noticed a swelling of the leg as high as the knee. She rested at home, and gradually the swelling subsided. On trying to walk, however, she discovered that her foot was very weak. About one week later a severe pain developed in the left antecubital fossa, striking down the centre of the arm and the radial two fingers and the thumb. She massaged both leg and arm herself, and it was not until three months after this onset of her trouble that she was examined and found to have "coldness of the limbs." Three months later still, muscle-wasting was noted in the hand and sensory loss of an indeterminate character. She was referred for a neurological opinion about 12 months after the beginning of the symptoms. By this time there had been a little improvement in her condition, and she was able to walk fairly well, but this improvement in walking resulted in the development of intermittent claudication in the left leg.

Examination revealed pronounced tortuosity and thickening of the peripheral vessels; left posterior tibial pulse not palpable; wasting of the left thenar eminence; loss of sensation to pinprick and cotton-wool in the distribution of the left median nerve; weakness of the evertors and dorsiflexors of the left foot, with a patchy loss to pinprick and cotton-wool in this area. The left ankle-jerk was absent. All investigations were normal with the exception of electrical testing. Electromyography showed lower motor neurone affection of the muscles supplied by the lateral popliteal and the left median nerves. Electrical stimulation showed partial reaction of degeneration. (The response to electrical stimulation of the medial popliteal group was normal.)

### Case 5

A woman aged 43 was seen on November 4, 1952, when she complained of a floppy right foot and pain in the right leg. Five weeks earlier she had developed a pain in her right calf on walking, and 48 hours later had noticed the extreme floppiness of the right foot. Examination revealed that the pulses were not palpable in either foot, though both femoral pulses were easily felt. The right foot, much colder than the left, was rather blue in colour and slightly oedematous. There was a severe foot-drop, with some impairment of power of the plantar flexion. The right ankle-jerk was absent. A little weakness was detectable in the muscles of the thigh, but the main affection was in the lateral popliteal group. There was a patch of anaesthesia about 3 in. (7.5 cm.) in diameter on the outer side of the leg surrounding the external malleolus.

She was given tolazoline, 50 mg. thrice daily, and since then has shown considerable improvement in the affected muscles. The foot-drop in particular was much improved, and her gait was normal, but she continued to have coldness and swelling of the affected leg.

### Case 6

A man aged 63 suddenly developed pain, exacerbated by walking, in his left calf. Twenty-four hours later his left foot became floppy, and he noticed numbness of the dorsal aspect of the outer three toes. After two weeks the condition began to improve, and when seen on December 19, 1952, he felt that it was almost normal. Examination showed: left foot colder than right; femoral pulses palpable; left foot pulses and right posterior tibial pulses absent; power in peronei and anterior tibials of the left foot reduced; posterior calf muscles normal; left ankle-jerk absent; no demonstrable sensory loss.

Further investigation could not be carried out, as a few days later he developed a sudden substernal pain and died at home.

### Case 7

A woman aged 70 had experienced intermittent aching pains at night in the left calf since 1951. In July, 1952, she noticed that even in the warm weather her left foot and lower part of the leg seemed unnaturally cold. Three months later she developed polyuria and polydypsia, and began to lose weight. In May, 1953, these general symptoms brought her to hospital, where a diagnosis of diabetes was made. In June she developed "floppiness" of the left foot and was sent to the neurological department, where physical examination revealed that, apart from bilateral cataracts, abnormalities were confined to the left leg. There was a moderate paresis of the anterior tibial and peroneal groups of muscles. The left ankle-jerk was diminished and there was impairment of sensation to pinprick and cotton-wool in an area some 2 in. (5 cm.) wide and 5 in. (12.5 cm.) in length surrounding the lateral malleolus. The left foot pulses were not palpable and the foot was cold.

She was provided with a suitable light toe-raising spring, and at the end of two months had recovered considerable power in the dorsiflexors of the left ankle. The foot was still cold, although the pulses could then be palpated. She has continued to improve.

### Case 8

A man aged 54 had a somewhat complicated medical history, mostly irrelevant to the present problem. Briefly, he was admitted to hospital in May, 1950, with lightning pains, Argyll Robertson pupils, and absent tendon jerks. His blood W.R. was positive, and C.S.F. analysis showed 49 cells, 50 mg. of protein, Lange 0112110000. The C.S.F. W.R. was also positive. Treatment with 14 mega units of penicillin in three weeks produced some improvement in the lightning pains, and allowed his C.S.F. chemistry to return to normal, although the W.R. remained positive in blood and C.S.F. two years after treatment. In March, 1952, he was admitted to another hospital for repair of a perforated duodenal ulcer (not a gastric crisis !), and during the subsequent treatment was given intravenous fluids into his right saphenous vein at the ankle (one week). After the drip was stopped his foot was swollen and he could not move his foot up or down. Two weeks later he was allowed up, and found that he could stand on his right leg but that the foot flopped about.

He was transferred to the neurological department four weeks after the operation. Examination of the right leg revealed the external popliteal palsy, with a patch of anaesthesia and analgesia over the outer side of the leg and dorsum of the foot. The ankle-jerk was absent. His

foot pulses could not be palpated on the right side, although they were easily palpable on the left. Electromyography showed a severe but incomplete lesion of the lateral popliteal nerve.

Massage and exercises were given, and a foot spring was provided. When seen four months later his condition was very much improved; although he still had some weakness of the peronei, he was otherwise recovered, and was able to walk normally. Eleven months after the paralysis his muscle power was normal, but he complained bitterly of his cold feet and said the right was worse in this respect than the left. His pulses could then (February 19, 1953) be palpated normally.

### Case 9

A woman aged 67 was admitted to a mental hospital on March 31, 1952, on account of involutional melancholia with paranoid trends (including a fear of being poisoned). During the course of treatment she was given an intravenous injection into the left saphenous vein, the leg being bound to a wooden back splint for a period of 48 hours. At the end of that time she developed some infection of the vein, and within the next two days a swelling of the left leg to a level above the knee developed. The observers are certain that at this time there was no evidence of foot-drop and that during the extreme activity which ensued the patient was moving all parts of all her limbs naturally and violently. By April 24 the swelling had almost subsided. She was sufficiently recovered mentally to be allowed up, but when she tried to walk on April 28 she had a definite left foot-drop. Immediate examination revealed, in addition to the paralysis with loss of power in the anterior tibials and peronei, an area of hypoaesthesia in the anterior tibial and musculocutaneous areas. The posterior tibial pulse on the left side could not be palpated, nor could the dorsalis pedis artery. On May 2 these findings were unchanged, though the area of sensory loss was much less extensive. The tendon reflexes were brisk and equal.

This patient, too, was given a foot spring, but no other treatment. During the next three months she improved steadily and when last seen had only a minimal weakness of the dorsiflexors of the foot.

### Discussion

The first seven cases described show a very definite association between the arterial occlusive lesion and the onset of the foot-drop. In Cases 8 and 9 the immobility of the leg required for maintenance of the intravenous therapy may have resulted in a compressive ischaemia of the lateral popliteal nerve of the type suggested by Sunderland (1945), but in both cases the onset of the foot-drop seems to have been separated from the infusion by several days, and in both cases a period of oedema of the leg intervened. Furthermore, in both cases there were the obvious vascular abnormalities and the absence of the peripheral pulses in the affected leg. Case 4 had the interesting median-nerve palsy in addition.

These cases illustrate the susceptibility of the lateral popliteal nerve to ischaemia of whatever origin, and indicate the predominance of motor affection with the relative paucity of sensory signs. The sensory loss was slight, and varied from case to case, but the manifestations of the foot-drop followed a constant pattern.

The question naturally arises regarding the reason for so much affection of the lateral popliteal muscles in contrast to retention of the medial popliteal function in cases in which the occlusion appears to have been of the popliteal artery. It is interesting, however, to note that in six of the nine cases the ankle-jerk was absent for a time at least. The medial popliteal nerve receives a fairly rich blood supply, stemming in part from the gluteal arteries and perforating branches of the femoral artery, with additional nutrient vessels entering at various points in the popliteal space and in the calf. The lateral nerve, on the other hand, receives only one nutrient vessel within the popliteal space (Sunderland, 1945). Bentley and Schlapp (1931) were able to show, in experiments on the sciatic nerve of the cat, that if the anoxic portion of the nerve exceeds 5 cm. considerable impairment of function of the nerve ensues. An occlusion of the femoral or popliteal artery therefore constitutes a much greater ischaemic threat to the lateral popliteal division than to the medial division, and, in particular, an obstruction at or just above the popliteal space itself will render the lateral nerve ischaemic over a critical length. Bentley and Schlapp also showed in their work that recovery of function is more rapid and complete in a nerve which has been rendered ischaemic than in one which has been subject to direct compression of its fibres. This fact accords well with the good functional prognosis for the local lesions described in our cases.

From the clinical point of view, the main feature is the benign prognosis of the local process, some degree of recovery being the rule and return to full power likely. The two deaths which occurred were attributable to the associated coronary disease. The most satisfactory line of treatment is the provision of the light elastic type of toe-raising spring during the period of paresis. Tolazoline and tocopherol acetate have been used, with a view to improvement in collateral circulation, but it is not possible to be certain about the exact benefits of such drugs.

### Summary

Nine cases are described in which a local vascular abnormality, either thrombosis or embolism of the femoral or popliteal arteries, was followed by foot-drop.

Attention is drawn to the vulnerability of the lateral popliteal nerve to ischaemia and to the underlying anatomical factors which may account for this.

Clinically the local condition is shown to be relatively benign and has a good functional prognosis.

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A new electronic clinical thermometer which gives an accurate temperature reading in five to seven seconds—less time than it takes to shake down the mercury in the ordinary type—was demonstrated recently at the Army Medical Service Graduate School, Washington. The electronic thermometer, known as the "Swiftem," has a thermistor (thermally sensitive resistor) attached at the tip of the delicate steel probe which replaces the old-fashioned glass mouthpiece. The recording meter and the mercury cell battery which supplies the power are contained in a plastic case small enough to fit easily into the palm of the hand. The thermometer is operated by a finger button switch and in appearance resembles a typical photographic light meter. Handpiece and thermometer are connected by a transmission cord, but its length does not affect the sensitivity or accuracy of the instrument. Its inventor, Colonel George T. Perkins, Director of the Dental Division of the U.S. Army Medical Service Graduate School, said it would be possible for a nurse to remain at her desk in the ward and take a patient's temperature in another part of the ward. The meter registers degrees of temperature in black figures below normal and red figures above normal. The steel probe is easily detached for sterilization, and tends to eliminate breakage and loss. It is claimed that the "Swiftem" represents the first change in clinical thermometers since the mercury-column type was introduced in 1867. In addition to recording a temperature much more quickly, the electronic one is more accurate in its readings.—*U.S.A. in Review*, June 25.

# ROULEAUX FORMATION INTENSITY OF PLASMA AND E.S.R.

BY

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The term "rouleaux formation intensity" (R.F.I.) is introduced to account for the different degrees of red-cell aggregation due to the effect of plasma factors on the erythrocytes.

It is generally agreed that the erythrocyte sedimentation rate (E.S.R.) corresponds to the R.F.I. of the plasma. This holds true if the Westergren (1921) technique is employed, but not necessarily with the use of the Wintrobe method (Wintrobe and Landsberg, 1935). Both methods may yield discrepant results. Values obtained with Westergren's method are thought to correspond more to the clinical condition of the patient than those secured with the Wintrobe technique. Davis (1946) cited cases with high Wintrobe but normal Westergren E.S.R.s. According to several reports (Gilmour and Sykes, 1951; Goldberg, Glynn, and Bywaters, 1952; Goldberg and Conway, 1952) the very opposite findings of high Westergren and normal Wintrobe E.S.R.s in many seriously ill patients occur even more frequently—for example, in cases in which the Westergren values were high, as anticipated, and the Wintrobe readings were normal or only slightly increased.

The following factors were believed to explain the discrepancy of findings by the use of the two methods: effect of the anticoagulant on the *p*H (Goldberg, Glynn, and Bywaters, 1952), the existence of the abnormal cryoglobulin in the plasma (Goldberg and Conway, 1952; Milles and Salt, 1952), the influence of diameter of sedimentation tubes (Milles and Salt, 1952), the so-called "reflux phenomenon" (Alexander, 1953), and the inhibition of rouleaux formation in deoxygenated blood (Duxbury, 1953).

This paper is a contribution to the discussion of the reasons for the discrepancy of findings with the Westergren and Wintrobe methods in an attempt to settle the question which method is preferable for clinical use.

## Methods

Blood samples were placed into tubes containing heparin (0.02 ml. of 5% pure heparin solution per 10 ml. of blood—that is, 0.1 mg. of heparin per 1 ml. of blood) or the powdered oxalate mixture of Heller and Paul (8 mg. of potassium oxalate and 12 mg. of ammonium oxalate per 10 ml. of blood).

Plasma and cells were then separated after centrifugation at 3,000 r.p.m. for 20 minutes. From each blood sample, eight mixtures or more were prepared, with a packed cell volume (P.C.V.) varying from 12.5 to 55%. Each of these mixtures, non-modified, or altered by the addition of one-fourth of its volume of 3.8% sodium citrate solution (1 ml. of mixture + 0.25 ml. of solution), was transferred into a calibrated Wintrobe haematocrit tube (100 mm. long, 3 mm. diameter) and maintained in a vertical position. For each blood sample, therefore, the sedimentation of at least 16 different combinations of cells and plasma was examined: eight mixtures of plasma and cells, and the same eight mixtures diluted according to the Westergren method. The comparison of the two methods is thus easy to be interpreted, since the blood, diluted and undiluted, is allowed to sediment in tubes of the same height and bore.

After E.S.R. readings were taken the tubes were centrifuged 30 minutes at 3,000 r.p.m. for P.C.V. determination. The P.C.V. of the mixture containing citrate solution is uniformly reduced to more than 20% compared with the corresponding undiluted mixture. Thus a very high E.S.R., approaching its maximum in one hour, gives a somewhat greater value in the diluted samples than in the undiluted.

For each sample a microscopical examination of rouleaux formation, the electrophoretic pattern of serum, and the fibrinogen content of plasma was made. The R.F.I. was estimated arbitrarily from observations of its occurrence in different fields, as follows: normal (N), slightly increased (1+), moderately increased (2+), and strongly increased (3+). For the sake of brevity, only the one-hour readings are reported here.

## Results

### 1. Comparison of E.S.R. with Undiluted and Diluted Blood of Varying R.F.I.

*Normal Plasma.*—When the P.C.V. is normal (45%) the E.S.R. of undiluted blood is very low (Fig. 1 (*a*)). However, as the P.C.V. is reduced the E.S.R. is strongly accelerated, reaching a high rate when the P.C.V. is very low. The E.S.R. of the same diluted blood is consistently lower, and the difference between the two becomes more pronounced the lower the P.C.V. becomes.

*Slightly Increased R.F.I. of Plasma.*—The E.S.R. of diluted blood is slower when compared with undiluted blood. Only when the P.C.V.s are very low or very high are the E.S.R.s equal (Fig. 1 (*b*)).

*Moderately Increased R.F.I. of Plasma.*—The E.S.R. of undiluted blood is very rapid and exhibits a new phenomenon, as shown in Fig. 1 (*c*). When the P.C.V. is very high (above 48%) the E.S.R. is suddenly lowered, as illustrated by the sharp bend of the curve. The E.S.R. of diluted blood is slightly lower than that of the undiluted when the P.C.V. ranges from 28 to 50%, and, on the contrary, slightly higher when the P.C.V. is either very low (less than 28%) or very high (about 50%).

*Strongly Increased R.F.I. of Plasma.*—The abrupt downward inflection of the curve shows that the sedimentation of undiluted blood is slowed down suddenly when the P.C.V. is within physiological limits (Fig. 1 (*d*)). When the P.C.V. is above 40% the E.S.R. values are low. On the contrary, the E.S.R. is very high when the P.C.V. is below 40%. This particular feature is not observed in the sedimentation of diluted blood: then the E.S.R. remains high and is always greater than in undiluted blood. The sudden downward bend of the sedimentation curve of undiluted blood stresses the important fact that the difference between the E.S.R.s of diluted and undiluted blood is particularly high when the P.C.V. is above 40%.

The above findings show that the E.S.R. is not necessarily proportional to the R.F.I. of the plasma. This is demonstrated with undiluted blood, especially in two conditions: (1) rapid sedimentation when the R.F.I. is normal and the P.C.V. is very low (Fig. 1 (*a*)), and (2) a very slow sedimentation when the R.F.I. is very strong and the P.C.V. exceeds 40% (Fig. 1 (*d*)).

### 2. Effect of Fibrinogen Content of Suspension Medium of Erythrocytes on the S.R. with Varying P.C.V.

It is well established that a correlation exists between the fibrinogen content and R.F.I. of plasma. The higher the fibrinogen content of a given sample the greater is the R.F.I. (Fahraeus, 1929; Zarday and Farkas, 1931; Kylin, 1935; Gray and Mitchell, 1942; Frimberger, 1942).

We examined the sedimentation rate of red cells suspended in plasma exhibiting strong R.F.I., in the serum from the same blood sample, and in mixtures of plasma and serum calculated to give fibrinogen contents of 20, 40, 60, and 80% of the total fibrinogen of the native plasma. Thus R.F.I. increases with increasing fibrinogen contents—

that is, the lowest R.F.I. is found in serum and the highest in native plasma. Fig. 2 shows the findings of E.S.R. plotted against fibrinogen content of the suspension medium with P.C.V.s of 45% and of 30%. The blood for this experiment was secured from a patient suffering from rheumatoid arthritis. The fibrinogen content of his native plasma amounted to 10 g. per litre, and upon electrophoretic analysis a marked increase of alpha and beta globulins was found.

Fig. 2 (*a*) shows that the sedimentation is very slow in the undiluted sample containing native plasma. Paradoxically, it is increased when the fibrinogen content is reduced. The curve has two maxima, and falls off at the lowest

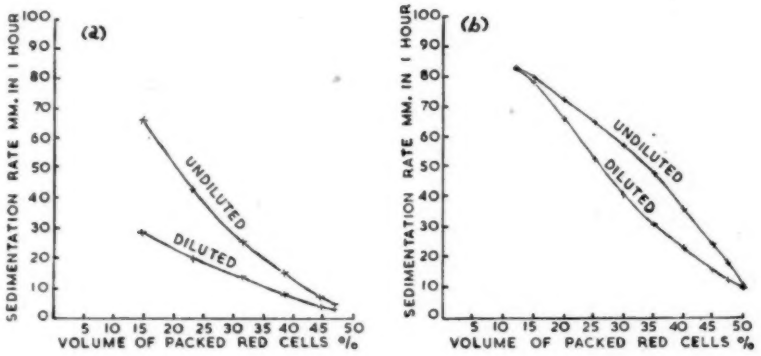


FIG. 1.—E.S.R. (one-hour readings) plotted against the P.C.V. of undiluted blood samples. The E.S.R. of diluted samples is plotted on the same vertical line as that of the corresponding undiluted sample. (*a*) Normal plasma. (*b*) Plasma with slightly increased R.F.I. (*c*) Plasma with moderately increased R.F.I. (*d*) Plasma with strongly increased R.F.I.

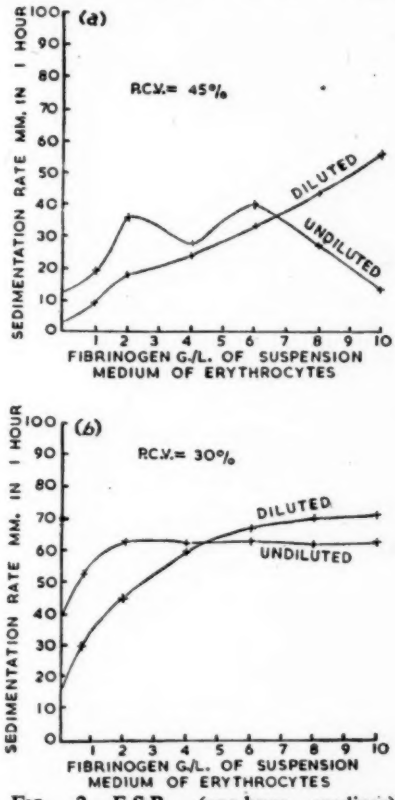


FIG. 2.—E.S.R. (one-hour readings) plotted against the fibrinogen content of the erythrocytes' suspension medium (see text). (*a*) The P.C.V. of undiluted samples is 45%. (*b*) The P.C.V. of undiluted samples is 30%.

fibrinogen content. However, when the same samples are diluted with the citrate solution the E.S.R. corresponds to the fibrinogen content of the preparation, reaching the highest value for the native plasma, while the undiluted samples show the lowest E.S.R. value. Thus the curve of the E.S.R. of undiluted samples demonstrates that in certain cases the lowering of the R.F.I. can accelerate the E.S.R. This paradoxical phenomenon, which may be compared to the "zone phenomenon" of immunology, does not occur under the following conditions: (1) when the samples are diluted in accordance with Westergren's method; and (2) when the P.C.V. is lowered to 30%, as shown in Fig. 2 (*b*), or less.

## Discussion

### 1. Causes of Discrepancy Between the E.S.R. of Undiluted and Diluted Blood

Three factors of unequal importance contribute to this discrepancy—that is, the variation of the P.C.V., the presence of plasma dilution, and the action of sodium citrate.

*Variation of P.C.V.*—We have shown that the P.C.V. of diluted blood is more than 20% lower than that of undiluted blood. Such a reduction in the P.C.V. tends to increase the E.S.R., and this is particularly important when the R.F.I. of the plasma is very strong (Fig. 1 (*d*)). For example, when the P.C.V. is reduced from 45 to 36%, a decrease of 20%, the E.S.R. is increased from 18 to 57 mm.

*Dilution of Plasma.*—The plasma is diluted to a great extent when citrate solution is added in the customary proportion of one-fourth of the volume of the blood sample. The plasma dilution is approximately one-third when the P.C.V. of the blood sample is 45%, and only one-fourth when the P.C.V. is 20%. The effect of this dilution on the E.S.R. differs according to the case. When the R.F.I. of plasma is normal, the dilution of plasma reduces the R.F.I. considerably—nearly to the point of abolishing it completely. However, when the R.F.I. of plasma is strongly increased it still remains rather high after dilution. Moreover, such a weakening of the R.F.I. can accelerate the E.S.R., as we have shown. It is understandable that under certain conditions—for example, high P.C.V. and high R.F.I. of a given blood sample—the dilution of blood has the cumulative effect of increasing the E.S.R., both in lowering the P.C.V. and the R.F.I.

*Action of Citrate Salt.*—It has been claimed that this salt inhibits rouleaux formation. We found that in the amounts employed in this study the action of this salt is insignificant compared with the two factors discussed above. These factors are sufficient to explain the differences observed between the E.S.R. of undiluted and diluted blood. A blood with a strong R.F.I. and a normal P.C.V. shows marked discrepancy in its E.S.R. according to the manner in which it is collected. Such blood, made incoagulable by dried heparin or the powdered oxalate mixture of Heller and Paul, has a low E.S.R. The same blood mixed with one-fourth its volume of 3.8% sodium citrate solution or with 7.6 mg. of powdered sodium citrate per ml.—the amount of salt used in the Westergren's method of dilution—gives a very high E.S.R. Thus the single fact of blood

dilution or its absence cannot explain the discrepancy of E.S.R. findings. Therefore the explanation must lie in variations of the P.C.V. The heparinized and the oxalated blood samples have their P.C.V. unchanged and their plasma undiluted. Conversely, the blood in citrate solution has a reduced P.C.V. and a diluted plasma. The blood mixed with powdered sodium citrate, although apparently undiluted, behaves like diluted blood : its P.C.V. is lowered because of cell shrinkage, and consequently the plasma is diluted by the intracellular fluid given off. Thus it is not the citrate salt itself which is responsible for the changes in the E.S.R., but rather the changes in the cell volume and plasma dilution.

The difference, therefore, in sedimentation between diluted and undiluted blood is essentially due to the simultaneous action of two factors : P.C.V. lowering and plasma dilution. When the R.F.I. of plasma is normal or slightly increased these two factors act in an inverse way. The increase of the E.S.R. due to the lowering of the P.C.V. is less than the lowering of the E.S.R. due to plasma dilution. Consequently, the E.S.R. of diluted blood is slower than that of undiluted blood. When the R.F.I. of plasma is strongly increased the accelerating effect of the P.C.V. decrease is marked, while the dilution of plasma has only a slightly decreasing effect or, sometimes, an accelerating action. Therefore sedimentation is much quicker with diluted than with undiluted blood.

The discrepancy between the E.S.R. of diluted and undiluted blood occurs under the following conditions : (1) slow E.S.R. of diluted blood with rapid E.S.R. of undiluted blood signifies a normal R.F.I. of plasma and a very low P.C.V. (Fig. 1 (*a*)) ; (2) slow E.S.R. of undiluted blood with very rapid E.S.R. of diluted blood signifies strong R.F.I. of plasma with a high P.C.V. (Fig. 1 (*d*)) ; (3) moderately increased E.S.R. of undiluted blood with very rapid E.S.R. of diluted blood signifies a strong R.F.I. of plasma with a P.C.V. between 30 and 45% (Fig. 1 (*d*)).

### 2. Clinical Significance of the E.S.R. of Diluted and Undiluted Blood

The E.S.R. test is employed in the clinic in order to detect approximately modifications in the protein composition of plasma. The degree of abnormality of plasma composition, shown by the increase of globulin and fibrinogen, corresponds to the degree of the R.F.I. increase of plasma. A method of measuring the E.S.R. cannot be useful to the clinician unless the E.S.R. values correspond to the R.F.I. of plasma. In the following it will be shown which of two techniques generally employed—blood undiluted (Wintrobe) and blood diluted (Westergren)—is more apt to give adequate information about plasma alterations.

First, let us suppose that the blood to be examined has a normal haematocrit value, averaging 45%. In normal plasma the sedimentation of undiluted blood is slow, but is rapidly accelerated with increasing R.F.I. of plasma, reaching the maximum when the R.F.I. is moderately increased. If the plasma change becomes still more pronounced, the E.S.R., far from becoming increased, is progressively decreased. As illustrated in Fig. 2 (*a*) the E.S.R. becomes very slow in plasma with the highest alteration, and therefore is misleading to the clinician. This is not the case when the blood is diluted by one-fourth its volume with sodium citrate solution. Here the E.S.R. increases progressively according to the degree of plasma alteration. It is slower in comparison with undiluted blood when the plasma is normal, and reaches a very high value when the plasma is greatly altered.

Let us suppose that the blood to be examined is anaemic, with a haematocrit reading of 30%. In the case of normal plasma this anaemic undiluted blood already has a relatively rapid E.S.R. A very small change in the protein composition of the plasma will bring the E.S.R. to its maximum, as shown in Fig. 2 (*b*). Further accentuation of the plasma change will not further modify it. With blood diluted one-fourth its volume by sodium citrate solution, the results are quite different. Dilution decreases the E.S.R. in the case of normal plasma, increases it in highly altered plasma, and shows that whenever the plasma is more abnormal the sedimentation is more rapid.

## Conclusion

In conclusion, the E.S.R. of undiluted blood is not a true mirror of plasmatic changes. If the haematocrit reading is low, the sedimentation rate of undiluted blood is high with a normal or slightly modified plasma. If the haematocrit is normal, the sedimentation of undiluted blood is slow in a highly altered plasma. The dilution of blood, independent of the haematocrit value, decreases the E.S.R. in the case of normal or slightly modified plasma, and increases the E.S.R. in the case of highly altered plasma. Therefore the E.S.R. findings of diluted blood give adequate information about the degree of plasma alteration. The Westergren method is more useful than the Wintrobe test, not because the tube of 200 mm. is employed, but because the blood under investigation is diluted.

## Summary

The apparent anomaly of a low sedimentation rate with the Wintrobe method and a very high E.S.R. with Westergren's method, as described by many authors, occurs consistently when the following conditions are present : a very strong rouleaux formation intensity (R.F.I.) of the plasma, and a packed red blood cell volume with an average normal value of 45% or higher.

The reason for this discrepancy between the two methods of measuring the E.S.R. lies in the fact that the sedimentation rate does not necessarily correspond to the R.F.I. of the plasma, but, on the contrary, becomes very slow under the two conditions mentioned above.

The addition of sodium citrate solution according to Westergren's technique masks this phenomenon in lowering the packed cell volume and in diluting the plasma.

The determination of the E.S.R. of diluted blood gives a more adequate account of the plasma abnormalities than does the determination with undiluted blood.

For clinical purposes, therefore, it is preferable to use Westergren's dilution method in tubes of 100 or 200 mm. length.

We wish to thank Dr. A. L. Copley and Dr. A. I. Suchett-Kaye for their helpful advice and criticism.

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A few weeks ago Miss M. P. HORNSBY-SMITH, Parliamentary Secretary to the Minister of Health, opened the newly built twin-operating-theatre suite at St. Mary's Hospital, Portsmouth. She said it was the largest capital scheme in the western area of the hospital service for the current year. The building cost was £40,997, and a further £10,000 was spent on equipment. The new theatre, together with the hospital's old main theatre, will serve some 224 hospital beds.

# BENETHAMINE PENICILLIN: A NEW SALT WITH A PROLONGED ACTION

BY

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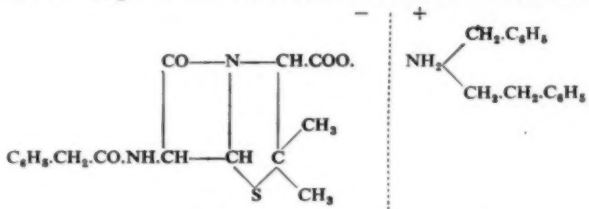
During the past ten years a great deal of research has been directed towards finding a method of giving penicillin that would be efficient and reliable and yet cause both patient and doctor the minimum of inconvenience. It has been found possible to increase the interval between injections by giving larger doses, by using less soluble salts, or by means of vehicles that delay absorption. Procaine penicillin, for instance, because of its low solubility, will maintain bacteriostatic penicillin blood levels for as long as twenty-four hours. In practice, however, many infections require treatment for four to six days, and a preparation with an even longer duration of action would have obvious advantages, since many cases could then be treated with only one or two injections. This paper describes the first clinical trials of a new penicillin salt that has been developed with this object in view.

## Chemical and Physical Properties

The approved name for the salt is benethamine penicillin ("benapen"). Chemically it is the N-benzyl-β-phenylethylamine salt of penicillin. Its structural formula is as follows:




It is a white crystalline compound, very slightly soluble in water (0.1% w/v at 40° C.). Its potency is approximately 1,100 units per mg. It is prepared as an aqueous suspension ready for injection in a vehicle containing suspending, buffering, wetting, and bacteriostatic agents.

## Pharmacology

Investigations that are being prepared for publication elsewhere have shown that benethamine penicillin is slightly less toxic than procaine penicillin when injected intravenously or subcutaneously into mice and rats. In mice the intravenous $LD_{50}$ is 170 mg. per kg., compared with 130 mg. per kg. for procaine penicillin. In the anaesthetized cat benethamine penicillin caused a greater fall of blood pressure and a smaller increase in respiration rate than the same weight of procaine penicillin. It can be administered orally to mice in doses exceeding 10 g. per kg. without causing any ill effects. No untoward reactions were observed in rabbits given single intramuscular injections of 100 mg., and macroscopic examination of the injected muscle after 72 hours revealed no signs of irritation other than slight hyperaemia.

During subacute toxicity tests on rats no ill effects or evidence of pain were noted when injections of 250 mg. per kg. were given into the same muscle daily for two weeks. This dose corresponds to nearly 30 times the expected dose in man. Post-mortem examination of these rats, killed after two weeks, revealed no abnormal changes in the viscera. Deposits of unabsorbed particles were found at the site of injection, and histologically these were surrounded by zones of foreign-body reaction.

## Serum Penicillin Levels

A co-ordinated trial was carried out at three hospitals to determine the serum levels attained after the intramuscular injection of different doses of the salt.

*Selection of Patients.*—The subjects chosen for the investigation were adult bed patients of average size with no fluid or electrolyte imbalance and no obvious evidence of renal disease. As indicated in the text, some healthy ambulant medical students were later included in the trial. Care was always taken to see that the individual had not recently been given any antibiotic that might interfere with the results of the assays.

*Method of Assay.*—Assays were performed on serum obtained by vein or ear puncture. The technique was that recommended by the U.S. Food and Drugs Administration Antibiotics Laboratory, Washington, D.C., with *Sarcina lutea* strain CP1–1001 as the test organism. For convenience, minor modifications were made as follows: (*a*) Holes (9 mm.) cut with a cork-borer were used instead of steel "penicillinders" on the assay plates. (*b*) The number of plates for each sample was increased from two to three. (*c*) Two dilutions of each serum were used—neat and 1/2 in *p*H 7 phosphate buffer. Standard solutions, usually 0.05 and 0.1 unit of penicillin per ml., were included on each plate. Since two dilutions of standard and unknown sera were used, the penicillin content of the unknown sera could be calculated from the zone of inhibition diameters by a method such as that recently described by Gaddum (1953).

## Results

Thirty-three bed patients were given a single intramuscular injection of 300,000 units (1 ml.). Individual and average assay results are given in Table I. Twelve patients

TABLE I.—*Penicillin Levels in units/ml. of Serum After a Single Injection of* 300,000 *units of Benethamine Penicillin Intramuscularly*

| Patient | Hours | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 3 | 6 | 24 | 48 | 72 | 96 | 120 |
| 1 | 0·95 | 0·23 | 0·22 | 0·07 | 0·03 | 0·01 | 0 | |
| 2 | 1·00 | 0·63 | 0·24 | 0·10 | 0·04 | 0·01 | 0 | |
| 3 | 0·44 | 0·52 | 0·40 | 0·19 | 0·09 | 0·05 | 0·01 | |
| 4 | 0·11 | 0·15 | 0·09 | 0·07 | 0·06 | 0·04 | 0 | |
| 5 | 0·14 | 0·07 | 0·18 | 0·03 | 0·03 | 0·03 | 0·01 | |
| 6 | 0·32 | 0·33 | 0·30 | 0·09 | 0·07 | 0·04 | 0·01 | |
| 7 | 0·06 | 0·05 | 0·06 | 0·05 | 0·03 | 0·03 | 0 | |
| 8 | 0·04 | 0·09 | 0·06 | 0·07 | 0·06 | 0·08 | 0·08 | |
| 9 | 0·25 | 0·11 | 0·24 | 0·11 | 0·03 | 0·03 | — | |
| 10 | 0·15 | 0·24 | 0·19 | 0·09 | 0·01 | 0·01 | — | |
| 11 | 0·10 | 0·22 | 0·10 | 0·08 | 0·01 | 0·03 | — | |
| 12 | — | — | — | 0·06 | 0·02 | 0·01 | 0·01 | |
| 13 | — | — | — | 0·05 | 0·03 | 0·04 | 0·01 | |
| 14 | — | — | — | 0·09 | 0·05 | 0·01 | 0 | |
| 15 | — | — | — | 0·11 | 0·04 | 0·05 | 0·03 | |
| 16 | — | — | — | 0·12 | 0·04 | 0·02 | 0 | |
| 17 | — | — | — | 0·13 | 0·10 | 0·10 | 0·06 | |
| 18 | — | — | — | 0·20 | 0·04 | 0·02 | 0 | |
| 19 | — | — | — | 0·09 | 0·04 | 0·03 | 0·01 | |
| 20 | — | — | — | 0·04 | 0·04 | 0·03 | 0·04 | |
| 21 | 0·07 | 0·08 | 0·10 | 0·06 | 0·05 | 0·04 | 0·05 | |
| 22 | 0·08 | 0·09 | 0·09 | 0·02 | 0 | — | — | |
| 23 | 0·21 | — | — | — | 0·08 | 0·07 | 0·04 | 0·03 |
| 24 | 0·36 | — | — | 0·16 | 0·06 | 0·05 | 0·02 | |
| 25 | 0·14 | — | — | 0·10 | 0·04 | 0·01 | 0·02 | 0·02 |
| 26 | 0·20 | — | — | 0·21 | 0·16 | 0·14 | 0·15 | 0·07 |
| 27 | 0·15 | — | — | 0·21 | 0·15 | 0·09 | 0·03 | 0·01 |
| 28 | — | 0·13 | 0·20 | 0·08 | 0·06 | 0·03 | 0·01 | |
| 29 | — | 0·15 | 0·20 | 0·12 | 0·10 | 0·09 | 0·05 | |
| 30 | — | 0·32 | 0·38 | 0·18 | 0·10 | 0·06 | 0·04 | |
| 31 | — | 0·06 | 0·07 | 0·04 | 0·04 | 0·03 | 0·04 | |
| 32 | — | 0·23 | 0·37 | 0·25 | 0·09 | 0·04 | 0·02 | |
| 33 | — | 0·20 | 0·27 | 0·12 | 0·07 | 0·06 | 0·05 | |
| Minimum | 0·04 | 0·05 | 0·06 | 0·02 | 0 | 0·01 | 0 | 0·01 |
| Maximum | 1·0 | 0·63 | 0·40 | 0·25 | 0·16 | 0·14 | 0·15 | 0·07 |
| Average | 0·26 | 0·21 | 0·20 | 0·11 | 0·06 | 0·04 | 0·03 | 0·03 |

— = Not tested.

received 600,000 units and 10 patients received 900,000 units. The results are given in Tables II and III. In Fig. 1 the average serum concentrations produced by the three doses are compared.

TABLE II.—*Penicillin Levels in units/ml. of Serum After a Single Injection of 600,000 Units of Benethamine Penicillin Intramuscularly*

| Patient | Hours | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 3 | 6 | 24 | 48 | 72 | 96 | 120 |
| 34 | 0·23 | 0·18 | 0·23 | 0·11 | 0·04 | 0·04 | 0·03 | 0·04 |
| 35 | 0·17 | 0·12 | 0·14 | 0·08 | 0·04 | 0·05 | 0·04 | 0·01 |
| 36 | 0·13 | 0·16 | 0·13 | 0·06 | 0·04 | 0·05 | 0·03 | 0·04 |
| 37 | 0·27 | 0·24 | 0·23 | 0·21 | 0·10 | 0·09 | 0·03 | 0·01 |
| 38 | 0·34 | 0·28 | 0·25 | 0·20 | 0·11 | 0·07 | 0·03 | 0·01 |
| 39 | 0·35 | 0·30 | 0·25 | 0·19 | 0·08 | 0·08 | 0·06 | 0·04 |
| 40 | 0·30 | 0·38 | 0·28 | 0·20 | 0·10 | 0·08 | 0·05 | 0·04 |
| 41 | — | — | — | 0·14 | 0·09 | 0·06 | 0·05 | 0·05 |
| 42 | — | — | — | 0·06 | 0·06 | 0·05 | 0·05 | 0·05 |
| 43 | — | — | — | 0·18 | 0·12 | 0·07 | 0·07 | 0·08 |
| 44 | — | — | — | 0·31 | 0·18 | 0·05 | 0·05 | 0·03 |
| 45 | — | — | — | 0·17 | 0·11 | 0·10 | 0·08 | 0·06 |
| Minimum | 0·13 | 0·12 | 0·13 | 0·06 | 0·04 | 0·04 | 0·03 | 0·01 |
| Maximum | 0·35 | 0·38 | 0·28 | 0·31 | 0·18 | 0·10 | 0·08 | 0·08 |
| Average | 0·26 | 0·24 | 0·22 | 0·16 | 0·09 | 0·07 | 0·05 | 0·04 |

— = Not tested.

TABLE III.—*Penicillin Levels in units/ml. of Serum After a Single Injection of 900,000 Units of Benethamine Penicillin Intramuscularly*

| Patient | Hours | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 3 | 6 | 24 | 48 | 72 | 96 | 120 |
| 46 | 0·40 | 0·53 | 0·40 | 0·39 | 0·32 | 0·31 | 0·17 | 0·09 |
| 47 | 0·21 | 0·26 | 0·34 | 0·22 | 0·11 | 0·07 | 0·03 | 0 |
| 48 | 0·25 | 0·25 | 0·23 | 0·21 | 0·10 | 0·08 | 0·10 | 0·07 |
| 49 | 0·17 | 0·17 | 0·14 | 0·14 | 0·10 | 0·06 | 0·05 | 0·04 |
| 50 | 0·24 | 0·32 | 0·18 | 0·14 | 0·09 | 0·08 | 0·09 | 0·09 |
| 51 | 0·18 | 0·18 | 0·26 | 0·14 | 0·08 | 0·06 | 0·05 | 0·03 |
| 52 | 0·20 | 0·25 | 0·22 | 0·11 | 0·07 | 0·11 | 0·08 | 0·08 |
| 53 | 0·44 | 0·45 | 0·31 | 0·11 | 0·08 | 0·07 | 0·06 | 0·06 |
| 54 | 0·28 | 0·33 | 0·21 | 0·11 | 0·07 | 0·07 | 0·05 | 0·04 |
| 55 | 0·11 | 0·12 | 0·18 | 0·05 | 0·05 | 0·05 | 0·05 | 0·05 |
| Minimum | 0·11 | 0·12 | 0·14 | 0·05 | 0·05 | 0·05 | 0·03 | 0 |
| Maximum | 0·44 | 0·53 | 0·40 | 0·39 | 0·32 | 0·31 | 0·17 | 0·09 |
| Average | 0·25 | 0·29 | 0·25 | 0·16 | 0·11 | 0·10 | 0·07 | 0·06 |

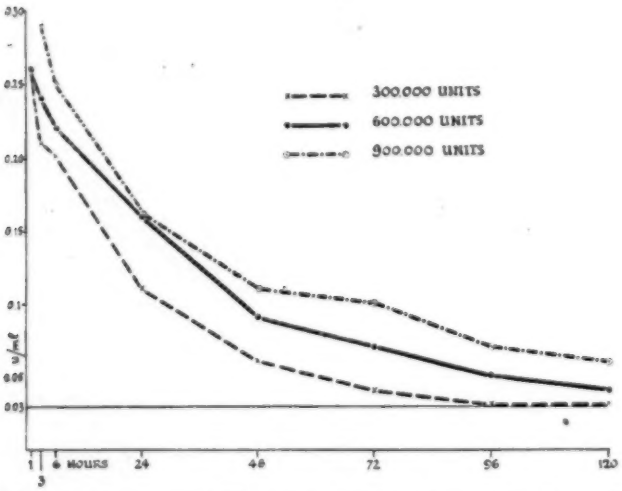



FIG. 1.—Serum penicillin concentrations after single doses of benethamine penicillin.

The effect of giving repeated doses was then investigated. Groups of six and seven individuals were respectively given 300,000 and 600,000 units intramuscularly on three alternate days. Assays were performed daily, starting 24 hours after the first injection. On the second and fourth days blood was taken before the injection was given, so that only the penicillin given 48 hours previously was assayed. The group receiving the three 300,000 units injections were bed patients as before, but the group given the three 600,000 units course were ambulant medical students. The results of these assays are given in Tables IV and V. Fig. 2 shows the average levels recorded.

TABLE IV.—*Effect of 300,000 units of Benethamine Penicillin Injected on Alternate Days.* Serum Levels in units/ml.*

| Patient | Days | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| 56 | 0·09 | 0·02 | 0·15 | 0·02 | 0·08 | 0·04 |
| 57 | 0·08 | 0·02 | 0·12 | 0·02 | 0·08 | 0·02 |
| 58 | 0·12 | 0·06 | 0·17 | 0·08 | 0·29 | 0·08 |
| 59 | 0·09 | 0·02 | 0·11 | 0·03 | 0·07 | 0·02 |
| 60 | 0·11 | 0·11 | 0·20 | 0·20 | 0·24 | 0·19 |
| 61 | 0·18 | 0·08 | 0·16 | 0·07 | 0·14 | 0·03 |
| Average .. .. | 0·11 | 0·05 | 0·15 | 0·07 | 0·15 | 0·06 |

* The injections were given on days 0, 2, and 4. On days 2 and 4 blood was taken for assay *before* the injection was given. The patients were in bed.

TABLE V.—*Effect of 600,000 units of Benethamine Penicillin Injected on Alternate Days.* Serum Levels in units/ml.*

| Patient | Days | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| 62 | 0·09 | 0·07 | 0·25 | 0·07 | — | — |
| 63 | 0·14 | 0·06 | 0·23 | 0·09 | — | — |
| 64 | 0·20 | 0·17 | 0·10 | 0·05 | 0·12 | — |
| 65 | 0·26 | 0·27 | 0·36 | 0·16 | 0·40 | — |
| 66 | 0·23 | 0·24 | 0·30 | 0·22 | 0·36 | 0·27 |
| 67 | 0·18 | 0·11 | 0·54 | 0·13 | 0·35 | 0·04 |
| 68 | 0·36 | 0·10 | 0·15 | 0·02 | 0·09 | — |
| Average .. .. | 0·21 | 0·15 | 0·28 | 0·16 | 0·26 | |

— = Not tested.

* The injections were given on days 0, 2, and 4. On days 2 and 4 blood was taken for assay *before* the injection was given. The subjects were ambulant volunteers.

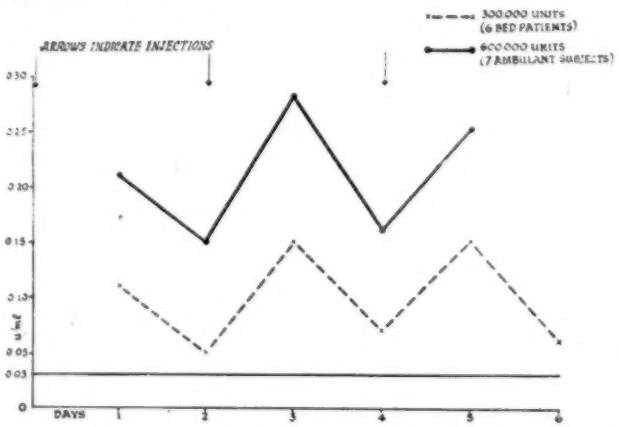



FIG. 2.—Serum penicillin concentrations after injection of benethamine penicillin on alternate days.

It will be seen from the tables and figures that the average penicillin serum concentration is maintained above 0.03 unit per ml. for four days after 300,000 units, for five days after 600,000 units, and presumably for six days after 900,000 units, but the level achieved during the first few hours is very similar whichever dose is given. Doses of 300,000 or 600,000 units given on alternate days did not appear to have a cumulative effect. They did, however, serve to confirm the impression that, notwithstanding considerable individual variations, doses of 300,000 units every two days or 600,000 units every three days could be relied on to maintain the penicillin in the blood at over 0.03 unit per ml. Other doses and longer intervals have not yet been investigated.

*Handling Properties.*—Although as a rule the suspension seemed easy to handle, syringe or needle blockage occasionally occurred in the earlier stages of the trial. This was found more likely to occur in syringes lubricated with paraffin or silicone lubricants. It very rarely happened with wet or even with dry unlubricated syringes. In consistency the preparation is very similar to aqueous suspensions of

procaine penicillin, and it can easily be withdrawn from the bottle and injected into the patient with a 20 or 22 B.W.G. needle.

*Side-effects.*—During these trials some 120 intramuscular injections of benethamine penicillin were given without any immediate untoward effects beyond the complaint in a few instances of a slight stinging pain or of some mild stiffness or aching at the site of injection. In five instances a more pronounced local reaction occurred later. One volunteer developed a "T.A.B.-like" reaction 72 hours after the injection of 300,000 units into the deltoid. This persisted for about 24 hours and then subsided. Four other ambulant subjects developed a hard tender lump in the buttock or thigh after the injection of 600,000 units; from one of these a small quantity of sterile necrotic material was evacuated. No general reactions occurred.

We have not yet had enough experience to be able to give an accurate assessment of the incidence of reactions, but it would seem a wise precaution to inject benethamine penicillin deeply into the largest muscle available, and preferably into the buttock.

### Discussion

Although no direct comparison was made, it is evident that in terms of blood levels benethamine penicillin falls between procaine penicillin (cf. Cohen, 1950) and benzathine penicillin (cf. Elias *et al.*, 1951; Fletcher and Knappett, 1953); that is to say, the levels are lower and more prolonged than those obtained with procaine penicillin but higher and of shorter duration than those that follow the injection of benzathine penicillin.

There was good agreement between the results at the three hospitals, but, as seems to occur with all repository preparations, there was considerable variation from patient to patient in the height and duration of the levels. The difference in the results of the three doses—300,000, 600,000, and 900,000 units—was surprisingly small, but on the whole the levels of the patients who received the larger doses were somewhat higher and more prolonged, and hence probably more efficient therapeutically. For instance, at 72 hours, 9 (27%) of 33 patients who received only 300,000 units had serum concentrations below 0.03 unit per ml., but none of the 22 patients who were given 600,000 or 900,000 units had levels below this figure at either 72 or 96 hours.

These results suggest that for the usual infections seen in everyday practice one injection, or possibly two, of 600,000 units for an adult or 300,000 units for a child should be adequate treatment. Although this investigation was not designed to test the therapeutic response to benethamine penicillin, our experience to date seems to indicate that this is the case. The salt has also obvious possibilities in the treatment of venereal diseases and yaws, for use before and after surgery, and in other forms of prophylaxis. It is clearly unsuitable for the treatment of infections that require a high concentration of penicillin, for which sodium penicillin remains the preparation of choice.

### Summary

Benethamine penicillin is a new relatively insoluble penicillin salt. After a single injection a bacteriostatic level of penicillin is maintained in the blood for three to six days, depending on the dose and the individual response. It is best administered by deep intramuscular injection into the buttock or thigh, where it is less likely to provoke any reaction than in the arm.

From a consideration of the blood levels it is suggested that one injection, possibly two, of 600,000 units for an adult or 300,000 units for a child should be adequate to treat the more sensitive and accessible infections seen in everyday practice, and our experience so far suggests that this is in fact the case.

We are grateful to Dr. A. F. Mohun for allowing us to include the results of his assays, and to him and to Dr. A. C. Cunliffe for their valuable criticism and advice. We also wish to thank Mr. Todd and Mr. Fleming for their technical assistance. Glaxo Laboratories Ltd. kindly supplied the benethamine penicillin. Finally, we should like to record our gratitude to the patients and volunteers who co-operated so willingly during this investigation.

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## ASSESSMENT OF 1,011 PATIENTS IN A MENTAL DEFICIENCY HOSPITAL

BY

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AND

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Research into various aspects of mental deficiency is in process at Prudhoe and Monkton Hospital. Our work is far from complete, but certain data are already available, and these may be compared with the results obtained by O'Connor and Tizard (1954) in their survey of patients in 12 mental deficiency institutions. Our classification of 1,011 mentally defective patients on clinical and psychometric grounds is at such variance with their figures that we think it may be of some interest.

In order to make it easy to follow and compare both sets of results at a glance we have arranged them exactly according to the pattern given by O'Connor and Tizard in Table II of their survey. We also attempted to follow their line of thought and took a group of 60 males and 24 females whose ages were between 16 and 30 years and who had been previously classified as feeble-minded, and we found their respective mean I.Q.s. Again the discrepancy between results is too wide to be ignored.

### Findings

The figures in Table I are based on clinical and psychometric findings. For clinical assessment the medical superintendent was responsible, and for psychometric assessment the clinical psychologist. In most cases clinical and psychological findings have been complementary; in a very few cases when discrepancy occurred, after full discussion of our findings, past history, social aspect, and behaviour of the case, the final classification was agreed upon.

TABLE I.—*Distribution of Patients by Sex, Grade, and Age*

| Age | Male | | | | Female | | | | Totals | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Idiot | Imbecile | F.-M. | Totals | Idiot | Imbecile | F.-M. | Totals | Idiot | Imbecile | F.-M. | Totals |
| 0–4 .. | 3 | 0 | 0 | 3 | 1 | 0 | 0 | 1 | 4 | 0 | 0 | 4 |
| 5–9 .. | 25 | 14 | 4 | 43 | 9 | 7 | 6 | 22 | 34 | 21 | 10 | 65 |
| 10–14 .. | 29 | 29 | 10 | 68 | 23 | 17 | 3 | 43 | 52 | 46 | 13 | 111 |
| 15 .. .. | 3 | 10 | 2 | 15 | 5 | 2 | 2 | 9 | 8 | 12 | 4 | 24 |
| Total (children) | 60 | 53 | 16 | 129 | 38 | 26 | 11 | 75 | 98 | 79 | 27 | 204 |
| 16–19 .. | 16 | 23 | 10 | 49 | 18 | 7 | 5 | 30 | 34 | 30 | 15 | 79 |
| 20–29 .. | 30 | 49 | 50 | 129 | 31 | 28 | 19 | 78 | 61 | 77 | 69 | 207 |
| 30–39 .. | 16 | 73 | 38 | 127 | 15 | 46 | 17 | 78 | 31 | 119 | 55 | 205 |
| 40–49 .. | 6 | 70 | 38 | 114 | 6 | 45 | 18 | 69 | 12 | 115 | 56 | 183 |
| 50+ .. | 6 | 46 | 14 | 66 | 4 | 43 | 20 | 67 | 10 | 89 | 34 | 133 |
| Total (adults) | 74 | 261 | 150 | 485 | 74 | 169 | 79 | 322 | 148 | 430 | 229 | 807 |
| Total .. | 134 | 314 | 166 | 614 | 112 | 195 | 90 | 397 | 246 | 509 | 256 | 1,011 |

The initial assessment was usually made on the admission of the patient to hospital, and was enlarged during routine examinations and examination before recertification. If necessary the matron or the chief male nurse and nursing staff were consulted with regard to the patient's social behaviour.

Every certified patient in the hospital was submitted to psychological testing; also, most of the licence cases were recalled to hospital for a short period so as to complete their assessment. Unfortunately, we were unable to get the assessment of all patients who were on the hospital books. Our list of exceptions includes 30 patients: 13 males and 3 females on licence, living over 100 miles from the hospital, one male patient who absconded from the hospital two years ago; one male and two female patients with whom we were unable to make any contact owing to superimposed psychosis from which they suffer; six male and two female blind patients; and one male and one female with gross speech defect. We have omitted the blind and speech-disorder patients purposely, as, although they have been assessed, we do not regard their assessment as fully valid, because of their physical disabilities. So out of a total number of 1,041 patients we have been able to secure data of 1,011 patients of both sexes who were on the hospital books on December 31, 1953. We have not included in our table data obtained from 68 patients who have been transferred or discharged, or have died since the beginning of our inquiry.

For the routine testing we used the revised Stanford–Binet intelligence scale F.L., the Alexander performance scale, the progressive matrices, and occasionally the Kent oral and Rorschach test.

We found the revised Stanford–Binet test, with all its shortcomings, still most useful when dealing with low-grade patients and children. The Alexander performance scale, beginning with 7 years' practical ability, was not so often used as the revised Stanford–Binet because of its limited range.

We found the progressive matrices of very limited value with mental defectives. We obtained only a few significant results with patients whom we would prefer to call socially or morally defective rather than mentally defective. However, we would like to mention that the behaviour and reactions of a patient when he is tested individually on matrices, irrespective of scores, can sometimes throw light on his personality. The Kent oral test we used very infrequently, and then mostly with blind patients.

Table II shows the results obtained on testing 84 feeble-minded patients by the revised Stanford–Binet intelligence scale F.L.; this particular test was chosen for our purposes because it agrees in most cases with the clinical assessment.

TABLE II.—*Distribution of I.Q.s of a Group of 84 Feeble-minded Patients Between 16 and 30 Years of Age*

| I.Q. | Male | Female |
|---|---|---|
| 50–54 | 22 | 8 |
| 55–59 | 11 | 4 |
| 60–64 | 11 | 3 |
| 65–69 | 4 | 4 |
| 70–74 | 3 | 2 |
| 75–79 | 1 | 1 |
| 80–84 | 4 | 1 |
| 85–89 | 1 | 1 |
| 90–94 | 3 | |
| Total | 60 | 24 |
| Mean I.Q. | 62·50 | 61·91 |

### Comparison with Another Series

Our results are compared with those of O'Connor and Tizard with regard to the classification of mentally defective patients and with regard to I.Q.s of a group of feeble-minded between 16 and 30 years of age (Tables III and IV). There may, of course, be quite a number of factors which are responsible for the discrepancy between two sets of results.

TABLE III.—*Difference in Classification and Percentage of Mental Defectives*

| | No. of Cases under Investigation | Idiots | | Imbeciles | | Feeble-minded | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % |
| O'Connor and Tizard .. | 592 | 35 | 5·9 | 247 | 41·7 | 310 | 52·3 |
| Present series .. .. | 1,011 | 246 | 24·3 | 509 | 50·3 | 256 | 25·3 |

TABLE IV.—*Difference of Method and Numbers and I.Q. Mean of Two Groups of Feeble-minded, Whose Ages are Between 16 and 30*

| | No. of Patients under Investigation | F.-M. Group Ages 16–30 Selected Group | F.-M. Group Ages 16–30 Actually Tested | Mean I.Q. Ages 16–30 |
|---|---|---|---|---|
| O'Connor and Tizard .. | 592 | 102 | 49 (group matrices) | 74–75 boys only |
| Present series .. .. | 1,011 | 84 | 84 (on R. Stanf.-Bin.) | 62·2 both sexes |

If the "sample" figures produced by O'Connor and Tizard give a true account of the actual population of the 12 mental deficiency hospitals under review, then it would appear that there are marked differences in approach to the question of mental defectives in hospital and perhaps different criteria concerning the function which a mental deficiency hospital is supposed to serve.

### Summary

The preliminary findings from the assessment of 1,011 patients in a mental deficiency hospital are discussed.

Comparison with the figures given in a similar survey, recently published, shows a wide variance in the results obtained.

REFERENCE

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## TREATMENT OF TETANUS WITH SUCCINYLCHOLINE

BY

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The first report on the use of muscular relaxant drugs in the treatment of tetanus was by Spencer Wells (1858–61), who in 1858 treated three cases with woorara (a crude preparation containing curarine). With the development of modern anaesthesia more such drugs have been introduced for the treatment of tetanus. Among these are curare (Godman and Adriani, 1949), gallamine triethiodide (Smith and Thorne, 1952), mephenesin (Hamilton Smith, 1953), and succinylcholine (Woolmer and Cates, 1952).

The case reported here was treated with continuous intravenous infusion of succinylcholine for five and a half days. For much of the time spontaneous respiration was so reduced that oxygenation had to be artificially maintained, and the case was dealt with in a manner very similar to that advocated by Lassen (1953) for the treatment of poliomyelitis with respiratory paralysis.

### Technique

Tracheotomy was performed as soon as it became obvious that the degree of relaxation required to overcome the spasms made artificial respiration necessary; the tracheotomy tube selected was fitted with a side-arm through which the gases used were delivered. Respiration was assisted by the

bag ventilation method. The mouth and nose were occluded with an anaesthetic mask.

For a large part of the time light anaesthesia was maintained with a mixture of 4–5 litres of oxygen and 2–3 litres of nitrous oxide per minute; additional sedation was obtained by the *ad hoc* administration of paraldehyde intramuscularly. The bronchi and pharynx were kept free of secretions by hourly aspiration, using a Jacques catheter attached to a Venturi sucker; at a later stage the foot of the bed was raised on a high trestle, the patient being supported by a strong cotton jacket attached to the foot of the bed by webbing straps. The trestle and jacket were made in the hospital, copied from a design suggested by Jacoby (1953). He was returned to the horizontal position from time to time for nursing purposes. Fluids were administered by the intravenous route, a "polythene" cannula leading from two bottles connected by a Y tube being used; one of these bottles contained 0.2% succinylcholine in glucose-saline, and the other glucose-saline or normal saline as required. Urine was collected for measuring the daily output with the help of a length of Paul's tubing. At some time during each day all drugs were withdrawn in order to assess the patient's progress. He was given soluble penicillin, 500,000 units twice a day, and A.T.S., 25,000 units daily. A member of the medical staff was with the patient throughout.

### Case Report

A farmer aged 42 pierced his right foot with a potato fork on August 24, 1953. He developed a spreading cellulitis, for which he attended his doctor on August 29; he was given penicillin and sulphonamides. The following day the local condition was showing signs of improvement; he was given 1,000 units of A.T.S. That evening he first noticed aching and stiffness of his back. The following day these symptoms were worse, and he was admitted to hospital in the evening. He had never been immunized against tetanus. On admission (August 31) he was seen to be a healthy and powerfully built man; there was continuous rigidity of the muscles of his neck, pectoral girdle, abdomen, and back, but there was no trismus and his limbs were relaxed. The small wound on the dorsum of his right foot had practically healed. He was given 100,000 units of A.T.S. intravenously and 100,000 units intramuscularly, morphine sulphate, ¼ gr. (16 mg.), and sodium amytal, 6 gr. (0.4 g.).

On the next day the first reflex spasm occurred; this was followed by others in increasing frequency and of greater severity, in spite of sedation with intramuscular paraldehyde and the administration of mephenesin both orally and parenterally. On September 3 treatment with succinylcholine was started.

*September 3.*—Treatment was started at 1 a.m. with the continuous intravenous infusion of a solution containing 0.2% succinylcholine. The spasms were kept within tolerable limits and respiration was not unduly depressed on a dose of 2–3 mg. of succinylcholine per minute; the more severe spasms tended, however, to break through. These were controlled by increasing the rate of infusion so that 15–20 mg. was given in a few seconds. This often produced severe respiratory depression, and the lungs were inflated with oxygen through a face-mask until spontaneous respiration was re-established. (At 9.30 a.m. a major convulsion occurred with opisthotonos, laryngeal spasm, and extreme cyanosis; muscular contraction caused obstruction to the vein which contained the cannula and arrested the flow of succinylcholine; 75 mg. was given by syringe into another vein and respiration was controlled as before.) Tracheotomy was performed at 12 noon; this gave far better control over respiration and enabled the bronchi to be cleared of secretions by suction. The patient was kept quietly asleep with the aid of a mixture of oxygen and nitrous oxide, respiration being assisted for most of the time. If the nitrous oxide were withheld he would wake up within a few minutes, and at times could take fluids by mouth. These periods of consciousness usually ended in a severe spasm which could be rapidly controlled by injection of 10–20 mg. of succinylcholine into the tubing of the intravenous apparatus. The maintenance dose of succinylcholine remained 2–3 mg. per minute.

*September 4.*—Treatment was continued on similar lines as before. During the day his pulse rate rose and he became progressively cyanosed; at 5 p.m. it was seen that the respiratory movements of the right side of the chest were diminished. A catheter was introduced to the limit of the right main bronchus and suction was applied. A large quantity of tenacious mucus was obtained and his condition improved as a result. Soon after this, a portable chest film showed segmental collapse in the right lower lobe. As a result of this it was decided to turn him on each side every hour and attempt to clear the entire bronchial tree by suction. Reflex spasms occurred unabated if the succinylcholine was withdrawn.

*September 5.*—His condition began to deteriorate, his pulse and respiratory rates rose, and cyanosis appeared. At the same time it was becoming difficult to keep the bronchi clear of secretions, and it was at this point that the foot of the bed was raised on the trestle. His condition soon began to improve, and, although much mucus was removed from the pharynx thereafter, little could be obtained from the trachea and bronchi. There was no sign of lessening of the spasms.

*September 6.*—His general condition and colour remained good, but during a trial without drugs a periodic respiratory rhythm appeared, similar to Cheyne–Stokes respiration, and muscular tone was seen to wax and wane in parallel with this rhythm. Complete relaxation accompanied apnoea, while powerful contractions occurred at the height of the respiratory phase. As the effect of the drugs wore off, so the muscular spasms became more pronounced, and within 15 minutes it was necessary to give further relaxant. Another phenomenon noticed this day was the appearance of peripheral circulatory collapse when the bed was lowered to the horizontal position; this was corrected when the bed was replaced on the trestle.

*September 7.*—His condition remained quite good, although it was noted that his ears had become cold and dusky; his pulse rate was labile and ranged from 85 to 125. In the evening he was without succinylcholine for one and a half hours, during which time he was given 10 ml. of intramuscular paraldehyde, but in the end spasms of such strength occurred as to require further relaxant. During this time he became conscious to the extent of being able to nod or shake his head in response to direct questions.

*September 8.*—Succinylcholine was withdrawn at 10.15 a.m., and at 10.40 a.m. he was given 10 ml. of intramuscular paraldehyde and the nitrous oxide was turned off. Apart from two short periods to cover the removal of secretions, no further succinylcholine was given. He was lowered by stages to the horizontal position. He did not recover consciousness, and the pulse rate rose to 140 and was of poor volume, the temperature began to rise, and respiration became rapid, shallow, and at times periodic in rhythm; he became deeply cyanosed. At 4.30 p.m. another portable chest film showed opacities in both upper lobes, the right being more extensive than the left. Large quantities of purulent sputum were aspirated from the bronchi. Muscular twitchings and periodic tightening of the pectoral and abdominal muscles occurred, but no severe spasms. Aureomycin, 500 mg. intravenously, was given six-hourly. He was turned on each side every hour and his back pummelled. The pulse rate reached 160 by 6 p.m.

*September 9.*—His condition gradually improved during the day, and he regained consciousness in the afternoon. Hourly turning and back-thumping was continued. Feeding was begun with milk fortified with "casilan" and glucose given through a Ryle's tube.

He gradually regained health and strength. The tracheotomy tube was coughed out on September 10. A chest film on September 11 showed complete clearing of the shadows seen on September 8. Muscular rigidity, which was partially controlled by oral mephenesin, persisted until September 20.

His right lower lobe collapsed on September 13, and this was re-expanded after a large quantity of purulent sputum was aspirated through a bronchoscope. He developed a deep venous thrombosis of the left leg on September 18 and anticoagulants were given for a week. He was discharged from hospital on October 2.

### Conclusion and Summary

The powerful, rapid, and short-lived action of succinylcholine would appear to make it the most useful muscular relaxant drug for the control of the reflex spasms of tetanus. It can rapidly overcome the severest convulsions, while full respiration and muscular power will return soon after it is withdrawn.

The case described was given a dose varying from 1.5 to 3 mg. per minute for five and a half days, with additional larger doses in times of difficulty; a total of 22.5 g. was given without toxic side-effects.

Light anaesthesia was maintained with nitrous oxide for most of the time; this produced restful sleep without any apparent untoward effects, but whenever it was withdrawn consciousness would return in a few minutes. It is interesting to note that the patient had no memory of the events which occurred during the period of treatment.

Adequate bronchial drainage was ensured by frequent aspiration through a tracheotomy tube, and by a high angle of tip.

My thanks are due to Dr. W. D. Brinton, under whose care this case was admitted, for his kind permission to publish this article; to Dr. R. P. W. Shackleton, whose advice as anaesthetist was paramount; to Mr. Gordon Midgley, who performed the tracheotomy; and to those members of the medical staff (consultant, registrar, and resident), who did their two-hour shift with the patient, day and night, for five and a half days.

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# Medical Memorandum

## A Case of Phaeochromocytoma without Hypertension

The following case of phaeochromocytoma, which did not fall into any of the usual categories, may be found of interest.

### CASE HISTORY

A builder aged 43 was first seen in April, 1952, and was admitted to hospital on four separate occasions between then and January, 1953, on account of recurrent vomiting. His attacks followed a similar pattern—he had a queer sensation in the epigastrium rising in the midline to the throat, he would have a shivering sensation starting in his legs and spreading upwards over the rest of his body, then he would be sick and would have epigastric pain going through to the back. Attacks of vomiting occurred two or three times daily for four to five days, after which he would remain well for about two months.

On examination the patient was rather hirsute and not wasted. He was restless during an attack, would throw off his bedclothes, would throw himself about the bed, and tended to adopt weird postures. His agitation at these times contrasted strongly with his normal quiet manner. His mucosae were pink; his skin was blotchy; pulse 84, temperature 99° F. (37.2° C.), blood pressure 95/55. There was no clinical abnormality in his cardiovascular, respiratory, or central nervous system. His abdomen was normal to palpation.

The history was not suggestive of peptic ulcer. Barium-meal examination showed nothing abnormal; occult blood was negative. In view of the vomiting the patient naturally became salt-depleted, his urinary and plasma chlorides were found to be low, and this was easily corrected by salting his drinks. The low blood pressure and vomiting suggested Addison's disease, but against this were his low urinary chlorides, his blood urea of 44 mg. per 100 ml., and a blood sugar of 130 mg. per 100 ml. His Wassermann and Kahn reactions were negative. On more than one occasion while in hospital his temperature varied between 99° and 100° F. (37.2 and 37.8° C.) and this was thought to point to a septic focus in the abdomen. His white-cell count was 19,000 per c.mm., but his midstream urine and cholecystogram were normal.

Eventual laparotomy was carried out on January 13, the findings being as follows: "The gall-bladder, stomach, duodenum, and left kidney were normal. There was a rounded and fairly soft mass about 2 in. (5 cm.) in its greatest diameter in the retroperitoneal tissue medial to the right kidney. This was enucleated without any great difficulty, and seemed to be closely associated with the right suprarenal gland."

*Histological Report.*—"Section shows a tumour consisting of irregular polygonal cells with oval vesicular nuclei. There is a piece of suprarenal cortex in the immediate vicinity of the tumour and many of the tumour cells exhibit a yellow pigment after fixation in chrome salts, thereby demonstrating that it is a phaeochromocytoma. There is no evidence of malignancy."

On his return to the ward post-operatively, the blood pressure was 65/30 and it had to be artificially raised for a fortnight by injections of adrenaline in oil and "eucortone." When discharged on February 7, 1953, the patient had no abdominal symptoms, there was no suggestion of recurrent pyrexia or vomiting, he had stopped all injections, and his blood pressure was 125/80. He has since continued to keep well.

### COMMENT

In a comprehensive review of this subject Walton (1950) divides the clinical picture of phaeochromocytoma into five categories: (1) paroxysmal hypertension, (2) persistent hypertension, (3) malignancy, (4) Addison's disease due to compression of the suprarenal cortex, and (5) asymptomatic. This patient cannot be said to fall into any of these categories. His blood pressure had been taken pre-operatively on no fewer than 12 occasions; it was usually around 125/70, often it was lower, on a solitary occasion it was 140/100. Swan (1951) has mentioned the problem of recognizing "the possibility that phaeochromocytoma is the cause underlying a story of paroxysmal disturbance in a patient with normal blood pressure when seen." Even during attacks this patient's blood pressure was normal. The only feature which could be considered to point to the diagnosis in this case was paroxysmal disturbance, which did not fit into any of the well-recognized clinical syndromes. In retrospect, the leucocytosis, the low-grade pyrexia, and the anxiety state are features that have been described in phaeochromocytoma, and direct questioning after the diagnosis was made revealed that the patient sweated a lot during strenuous exercise and also with his attacks of vomiting.

This history, however, seems to suggest that, in an otherwise healthy person, paroxysmal disturbance, even in the absence of paroxysmal hypertension, should make one think of phaeochromocytoma.

I thank Dr. J. W. Todd and Mr. S. C. Raw for permission to publish this case, which was under their care; Dr. C. C. Thomas for the histological report; and Dr. E. H. Hemsted for helpful advice.

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# Reviews

## EVOLUTION

*Evolution as a Process.* Edited by Julian Huxley, F.R.S., A. C. Hardy, F.R.S., E. B. Ford, F.R.S. Contents consisting of contributions by 19 people. (Pp. 367; illustrated. 25s.) London: George Allen and Unwin Ltd. 1954.

The question is sometimes asked whether first-year medical students need be exposed to courses in botany and zoology, and the question is sometimes answered by the assertion that these subjects are useful prerequisites for a medical degree. They may be, but there are much more important reasons than that for including them in the medical curriculum, and one of the reasons is evident from an inspection of this book. The idea of evolution is not a recondite concept like the divine right of kings, which no one but specialists need bother to understand. Nor is it a landmark of history like the Reform Bill, which was important a century ago but is now only of antiquarian interest. It is still the most fascinating problem of biology, and the most fruitful idea which has ever confronted biologists; and a man who does not understand the rudiments of it has no right to call himself civilized.

In five years we shall celebrate the centenary of the publication of Darwin's *Origin of Species.* In essentials his theory still stands, though it has not stood still. In this book nineteen distinguished biologists describe the present state of evolution in their special fields. Among the essays are the following: "Relation between the evolution of central nervous functions and the body size of animals" (Bernard Rensch), "Colour vision and its evolution in the vertebrates" (E. N. Willmer), "Memory, heredity and information" (J. Z. Young), "Correlation of change in the evolution of higher primates" (S. Zuckerman). The essays are written for biologists and it is perhaps too much to hope that many medical men recollect enough first-year biology to read the work without effort. But the effort is worth while. Here is Darwin's germinal idea applied to subjects as diverse as cuckoo's eggs, memory, courtship in birds, colour blindness in man, and the differences between the way men and gorillas wear out their teeth. The essays are all authoritative, though they inevitably differ in lucidity. They are an exciting summary of contemporary knowledge, and a gracious compliment to the sixty-fifth birthday of Julian Huxley, whose grandfather was "Darwin's bulldog" and who himself has made massive contributions to the study of evolution.

E. ASHBY.

## STERILITY AND FERTILITY

*Mammalian Germ Cells.* A Ciba Foundation symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. (Pp. 302; illustrated. 30s.) London: J. and A. Churchill. 1953.

The Ciba Foundation Symposia comprise a small invited international gathering of experts who not only contribute a series of papers on recent original work but also participate freely in an informal discussion following each paper. These discussions often contain information as valuable as the papers themselves, and both are reported fully in the present volume.

The symposium is in two parts dealing respectively with spermatozoa and with ova. There are several papers on the significance and occurrence of various amino-acids and of fructose and other sugars in mammalian semen. It is shown that aspermia, induced in bulls by warming the scrotum, leads to an increased excretion of 17-ketosteroids and of other steroids. Even transport of a bull for 10 to 20 miles may cause adrenal cortical overaction and damage to spermatogenesis. The effect of streptomycin on bull semen is discussed and the proteolytic enzymes of human semen are reviewed. An important section is concerned with sperm preservation at low temperature. Spermatozoal movement is extensively discussed and so is the effect of varying periods of continence on the quality of human sperm. Chicken-pox is reported to cause a temporary aspermia.

Later sections deal with controlled ovulation in farm animals and with the factors influencing the formation of first and second polar bodies; some excellent illustrations are presented here. Attempts to preserve rabbit ova at low temperature are described. Two final sections on the role of post-coital tests in human fertility clinics present very divergent views and should be of much interest to all concerned with such clinics.

This volume of collected papers should prove of the greatest interest both to those concerned with fertility and sterility clinics and to those who have to do with the breeding of farm animals.

C. L. COPE.

## DENTAL SURGERY

*Surgery for Dental Students.* By M. F. A. Woodruff, M.D., M.S.(Melb.), F.R.C.S.(Eng.). Foreword by S. H. Wass, M.S.(Lond.), F.R.C.S.(Eng.). (Pp. 326; 108 figures. 30s.) Oxford: Blackwell Scientific Publications. Springfield, Illinois: Charles C. Thomas. Canada: The Ryerson Press. 1954.

This is a clear and well-illustrated book, which should prove of considerable value to dental students. It is always difficult in writing a book of this type to avoid overlap when discussing conditions which are already adequately dealt with in the students' course in oral and dental surgery. The author, to a large extent, has avoided this pitfall, and, if anything, any criticism is concerned more with omissions. Thus it is surprising, after discussion of different forms of cysts, to find that odontomes are dismissed in a single paragraph as being relatively rare in man. There are also minor criticisms of statements, such as that the lining of the cysts in adamantinoma consists of either squamous or columnar epithelium, when it is held by the majority of dental pathologists that the presence of columnar epithelium sharply differentiates the adamantinoma from the dental cyst lined with squamous epithelium. All would not agree that lozenges containing penicillin should not be used in fuso-spirochaetal gingivitis, since they are a valuable treatment in the first 48 hours. The discussion on focal sepsis also does not fully accord with modern views. These criticisms mentioned, as well as some others, give a slight impression of lack of co-operation in writing the book, but they in no way detract from the value of the book in giving the student a sound insight into the main principles of general surgery.

ALEXANDER MACGREGOR.

## DIABETES

*Experimental Diabetes and its Relation to the Clinical Disease.* A Symposium organized by the Council for International Organizations of Medical Sciences, under the auspices of Unesco and W.H.O. Consulting editors, J. P. Hoet, F. G. Young. Editors for the Council, J. F. Delafresnaye, G. Howard Smith. Foreword by J. Maisin. (Pp. 352; illustrated. 35s.) Oxford: Blackwell Scientific Publications. 1954.

There has been urgent need for a comprehensive and critical review of the work which has been done on experimental diabetes in animals and its relation to clinical diabetes. No better account can be provided than that found in this book, which records the proceedings of a symposium sponsored by the Council for International Organizations of Medical Sciences in the summer of 1952. The detailed discussions which follow each paper provide more valuable criticism than would be possible in a volume written by a single worker or group of workers.

After a useful review of the histology of the islets of Langerhans by Best, papers on glucagon by de Duve and

Candela are critically discussed. The account of the mechanism of the action of alloxan and other chemical diabetogenic agents is particularly good, although the suggestion by Gaarenstroom and by Loubatieres that alloxan may occur naturally and play some physiological role in carbohydrate metabolism was quite clearly regarded as unproved, as was the role of uric acid in producing diabetes. A series of communications consider in detail the interrelationships between the anterior pituitary and pancreatic and adrenal hormones in the control of carbohydrate, protein, and fat metabolism. This section may well be read in conjunction with the recently published Ciba Foundation Colloquium on Endocrine Inter-relationships in Carbohydrate Metabolism. Obesity with or without a genetic factor in the aetiology of diabetes was emphasized by Dr. Hannsen and by Dr. Lawrence, who classified diabetes into insulin-deficient, lipo-plethoric, and lipo-absorptive types. In a stimulating paper by Professor Hoet, and in its following discussion, emphasis was laid on the need for future investigations into the effect of pregnancy on diabetes. The volume concludes with a brief but excellent survey of the position at the time of the conference by Professor F. G. Young, who with Professor Hoet has been a consulting editor of this volume.

The book should be read by all workers in diabetes whether interested from the clinical or the experimental points of view. The symposium reveals that in spite of the vast amount of work in both the clinical fields and in the laboratory the mechanism and cause of human diabetes is wrapped in even greater mystery than it was twenty-five years ago, when all seemed so simple and straightforward. Although the symposium was held nearly two years ago, the account appears remarkably up-to-date.

C. H. GRAY.

## PHYSIOLOGY OF THE HEART

*Physiological Cardiology.* By Arthur Ruskin, M.D., F.A.C.P. American Lecture Series No. 184. A Monograph in the Bannerstone Division of American Lectures in Physiology. (Pp. 318; 12 illustrations. 57s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1953.

It is agreed that "attempts to bridge the gap between experimental physiology and clinical medicine are always in order," and that the physiological approach to practical cardiology "leads to more rational and progressive case management." But whether or not this book fulfils its purpose is another matter.

In the first place it is not well written, which comes as a jar to readers who have enjoyed the masterly prose of the great physiologists. A typical sentence reads as follows: "Clinically, the difference between the slightly elevated roentgenkymographic (total) and the slightly diminished Fick (aortic) outputs accounts for a regurgitation of 25 to 50% of the left ventricular stroke volume." While one should be careful in criticizing a mode of expression in a foreign language, I feel sure that what happens in mitral incompetence could be more simply described.

Of the rhythm changes, heart block was chosen for scrutiny. What can be said of this kind of help? "When simultaneous contractions of the atria and ventricles occur, large *a* plus *c* waves are seen in the jugular pulse and the first heart sound is markedly accentuated (cannon ball)"—page 9. Cannon waves in the jugular pulse are again regarded as a summation effect on p. 5.

Congestive failure is an excellent field for the physiologist, but can the situation be clarified by sentences such as these? "From the standpoint of cardiodynamics, 'low output' failure may be called pressure and flow failure, 'high output' failure—pressure, but not absolute flow, failure"—page 37; "In man the pulmonary arterial and right ventricular pressures in hypertensive left ventricular failure, as in compensated mitral stenosis and cor pulmonale, show only elevations in the systolic (e.g. up to 100 mm. Hg) and pulse pressures . . . when right ventricular failure supervenes, the diastolic and mean, as well as the systolic pressures, in the pulmonary artery and right ventricle become constantly elevated"—pages 45–46; "Dilating right heart chambers show larger increments in the pressure/volume ratio than the undistended chambers"—page 46; "Increased diastolic and mean pressure within the over-dilated failing left atrium lead easily, because of absence of valves in the thoracic veins, to pulmonary venocapillary distension and stasis. An increased blood volume and venous return, in the presence of minute lowering of the output of the left heart as compared to the right (this discrepancy is soon replaced by a new steady state of equally lowered stroke volumes) like-wise overdistend the heart chambers and pulmonary vessels. As shown in animal experiments and human subjects, the pulmonary venous, capillary and arterial pressures rise. The right ventricular diastolic pressure is yet normal. The diminished inflow into the left atrium is thus augmented and the pulmonary congestion is relieved"—page 48.

Another fruitful field for the physiologist is the haemodynamics of mitral valve disease. Here we have: "The shortened systole is manifested by a loud closure of the thickened, still unfused, mitral cusps—a loud snapping first heart sound. The second pulmonic sound is loud and split, because of pulmonary arterial dilatation, hypertension, and consequent forceful closure of the pulmonic, earlier than the aortic, valve"—page 176. After discussing the effect of heart rate on left ventricular filling in mitral stenosis a new paragraph under the title of "Therapeutic Considerations" opens with: "Digitalis beneficially slows the heart rate, but, after an initial rise, the cardiac output falls, with elevation of the pulmonary vascular and right ventricular pressures, indicating increased pulmonary congestion." There is no comment on the treatment of acute pulmonary oedema in mitral stenosis—fascinating from the physiological point of view.

There is little point in citing further examples to illustrate that this bridge between experimental physiology and clinical medicine does not invite a tired traveller; the physiological approach is presented a great deal more clearly, and often more accurately, in several standard textbooks of cardiology.

PAUL WOOD.

## SURGEON AND CHRISTIAN

*Arthur Rendle Short: Surgeon and Christian.* By W. M. Capper and D. Johnson. (Pp. 208; illustrated. 8s. 6d.) London: Inter-Varsity Fellowship. 1954.

Arthur Rendle Short was the son of good Nonconformist parents, and had to make his own way in the world. He had brains and industry, which enable him to win scholarships, gold medals, and prizes, to take a B.Sc.Lond. with first-class honours in geology, to study at the University of Bristol and University College Hospital, London, to qualify with honours (M.B. and M.D.) at London University, and to take the F.R.C.S. Disappointed in his desire to become a medical missionary, he specialized in surgery, eventually becoming professor of surgery at the University of Bristol and surgeon to the Bristol Royal Infirmary. He achieved a high reputation as an operating surgeon and teacher.

This book by two of his medical friends is based on material and notes kept by Short for the purposes of an autobiography. It contains descriptions of life in the Bristol hospitals in the early days of the century, sketches of personalities in the Bristol Medical School, and many of the humorous anecdotes which Short used to tell his students. He wrote *The New Physiology*, which passed into several editions, many surgical papers, including those on the aetiology of appendicitis, and edited the surgical section of the *Medical Annual*. Short had a deeply religious frame of mind, and much of the book is devoted to his self-sacrificing work for others, his preaching, his writings on religious subjects, in which science fortified religion, and his influence with evildoers to mend their ways. He was not only a good surgeon, but also a Christian warrior. This account of a well-spent life will appeal to all medical men and especially to those who worked with Rendle Short.

ARTHUR S. MACNALTY.

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## BLOOD GROUPS AND DISEASE

Studies of the relation between blood groups and diseases (other than transfusion reactions) may be divided into two main classes—those concerned with the blood groups only of affected individuals, and those concerned with the blood groups of both mothers and their foetuses in relation to the diseases of either or both. Restricting consideration to the classical or ABO blood groups, we have in the first class studies on the effects of the antigens A and B (and possibly O), as such, on morbidity; in the second class we have studies on the effect of the antigens present in the foetus in stimulating the production of agglutinating or haemolytic antibody in the mother, or, conversely, the effect of an existing maternal antibody in damaging the foetal red cells which bear the corresponding antigen. Studies of the relation between mother and foetus began as early as 1905, when Dienst[1] first showed the immunizing effect of foetal cells containing the A or B antigen on a mother who lacked that antigen. Despite the diversion of attention to the probably more important Rh blood groups, work on this aspect of the ABO groups has continued at intervals since the time of Dienst's announcement. It is only much more recently that serious consideration has been given to the possibility that persons of different ABO groups might differ intrinsically in their susceptibility to certain diseases.

The *Journal* this week contains three papers on the relation of blood groups to disease. All of them set out the results of statistical studies on the blood group frequencies in selected classes of sufferers as compared with those in the general population. The relative frequency of neoplastic diseases and of peptic ulcer in persons of different blood groups almost certainly depends entirely on individual susceptibilities: any persistent effect of maternal antibodies in the adult life of the offspring is extremely unlikely. In a paper which is a model of diagnostic and statistical rigour, Professor Ian Aird and his colleagues show this week even more clearly than before[2] that persons of group A have a greater susceptibility to carcinoma of the stomach than those of other blood groups, and these authors bring to light the even greater relative susceptibility of persons of group O to peptic ulcer. In contrast, they have also shown that there is no statistically significant excess of any of the blood groups among sufferers from carcinoma of the colon and rectum, of the bronchus, and of the breast. Their results for cancer of the bronchus are supported by the similarly negative results of Drs. R. B. McConnell and C. A. Clarke and Mr. F. Downton in their study of blood-group incidence of carcinoma of the lung, though for oat-cell and oval-cell carcinomas taken together there was a barely significant excess over normal in the A : (A + O) ratio. Apart from the papers published in the present issue, and the previous work of Aird, Bentall, and Roberts,[2] perhaps the most important previous study in this field is the demonstration by Struthers[3] of an excess of group A among children dying with bronchopneumonia. As Aird and his colleagues point out, this type of research is still at an empirical stage and the main need is for statistics of blood group frequency in numbers of other diseases. But it is important that clear-cut and widely accepted pathological entities be studied, with rigidly defined diagnostic criteria. Even relatively small series conforming to these requirements are worth publishing in brief notes—in contrast to extensive unsupported speculations. Working hypotheses there must be, however, and a certain amount of speculation is to be welcomed when important new data are published.

The fact that two of the diseases which show an excessive susceptibility in persons of a single blood group are connected with the stomach suggests that the secretion of blood group substances by the stomach may be involved. About 75% of persons secrete their particular blood group substance in both saliva and gastric juice, and the ability so to secrete is genetically determined. It is important, therefore, to know the secretor status as well as the blood group of persons suffering from the various diseases, and Aird and his colleagues have in fact made plans to collect such data. It is important, furthermore, to try to determine whether the one blood group substance is actively pathogenic or whether the other substances are protective. Such knowledge may ultimately prove to be of value for prophylaxis and treatment of the diseases concerned.

[1] *Zbl. Gynäk*, 1905, **29**, 353.
[2] *British Medical Journal*, 1953, **1**, 799.
[3] *Brit. J. soc. Med.*, 1951, **5**, 223.
[4] *British Medical Journal*, 1954, **1**, 1197.
[5] *The Rh Blood Groups and their Clinical Effects*, 1948, M.R.C. Memorandum, **19**, p. 48.
[6] Waterhouse, J. A. H., and Hogben, L., *Brit. J. soc. Med.*, 1947, **1**, 1.
[7] Bussard, A., and Eyquem, A., *Ann. Inst. Pasteur*, 1947, **73**, 1194.
[8] *Biol. Rev.*, 1945, **20**, 73.

The third paper, by Drs. L. A. Pike and A. M. Dickins, shows the existence of a marked, and statistically significant, excess of mothers of group O among those suffering from toxaemia of pregnancy. So far as the published data go, the excess might be explained by a direct effect of the maternal antigen, uninfluenced by that of the foetus, on the susceptibility of the former to toxaemia. But on the whole it is more likely that, as the authors suggest, the foetal blood group plays some part in the aetiology. Most previous studies on blood groups in relation to pregnancy have been concerned with possible harmful effects of the maternal antibodies on the foetus in a heterospecific pregnancy—that is, one in which the foetus possesses one of the blood group antigens A or B which is lacking in the mother. This aspect of the subject has been fully considered in these columns recently,[4] but little attention has hitherto been paid to possible injury to the mother. In the parallel case of Rh blood group incompatibility, Mollison[5] has pointed out that in the very severe cases in which the infant is hydropic there appears to be a special tendency to toxaemia in the mothers, but this does not occur when the disease in the infant takes one of the rather less severe forms. A few previous workers, beginning with Dienst, have suggested that the entry of ABO incompatible foetal blood into the mother's circulation was a cause of toxaemia, but no convincing evidence has ever been brought forward. As Pike and Dickins point out, however, the symptoms of pregnancy toxaemia are not unlike those of an incompatible transfusion. In view of the supporting evidence given by the maternal blood group statistics collected by these authors, it is important that further studies should be instituted taking into consideration the blood groups of both mothers and foetuses. Since even in presumably normal pregnancies the frequencies of the blood group combinations of mothers and offspring may differ significantly from those predicted by elementary genetical theory,[6] the question of controls in such a survey will demand careful attention. A further point which needs investigation is whether the chemical and serological similarity between gonadotrophic hormone and blood group A substance[7] has any bearing on the hormonal changes which occur in toxaemia.

Whatever may prove to be the reasons for these connexions between blood group and disease, they have profound implications for human evolution, since they provide part, at least, of the means long predicted by Sir Ronald Fisher and Dr. E. M. Ford[8] whereby an active equilibrium may be maintained over many generations between the frequencies of the different blood groups.

## VIRUS CHEMOTHERAPY

In 1944 Kramer, Geer, and Szobel[1] published a review of all virus chemotherapy literature which had appeared up to that time, and were impressed by the uniformly negative nature of the results except in the psittacosis-lymphogranuloma group of viruses. To-day, ten years later, there is scarcely any more ground for optimism, for almost the only solid achievement which has emerged from a vast amount of work is the discovery by Hamre, Bernstein, and Donovick,[2] and confirmation by Thompson, Price, and Minton,[3] that certain thiosemicarbazones are active against vaccinia virus growing in mice and eggs. It is therefore appropriate at the present time to take stock of what is being done and try to ascertain why so little is coming of it. Pharmaceutical houses in Britain and the United States are deeply committed to programmes of antiviral screening, and other research laboratories are constantly engaged in testing natural products and known organic compounds for antiviral activity. Most of this effort is directed against influenza virus, since it is a virus of great economic importance and also amenable to study in small laboratory animals; but there is still no sign of any treatment likely to be of clinical importance. The onlooker may be tempted to speculate that in the anxiety to obtain results the suitability of the methods may have received insufficient attention.

Influenza virus is usually inoculated into the allantoic cavity of fertile eggs, and the compound to be tested for antiviral activity is injected by the same route. The eggs are incubated for a further period to allow the virus to multiply, and the amount of new virus liberated into the allantoic fluid is determined by haemagglutination titration. The finding of an amount of virus significantly less than that produced in a control group of eggs not treated with the compound is taken as an indication that the compound possesses antiviral activity. An experiment of this type is easily carried out and the procedure is widely used; recently Takemoto, Robbins, and Smith[4] found that twelve unrelated synthetic compounds had some antiviral activity when thus tested. The method has serious theoretical defects, however, which render it unsuitable in spite of its convenience. For instance, virus and test compound are both injected into the allantoic fluid and there incubated together for 48 hours or so; there is thus ample opportunity for chemical inactivation of the virus to occur, and the method is little better than an

[1] *J. Immunol.*, 1944, **49**, 273.
[2] *Proc. Soc. exp. Biol. (N.Y.)*, 1947, **73**, 275.
[3] Ibid., 1951, **78**, 11.
[4] *J. Immunol.*, 1954, **72**, 139.

*in vitro* test. The allantoic cavity is, moreover, an excretory cavity, and substances injected into it are not likely to enter the circulation and approach the allantoic membrane by the proper route. This objection can be met to a certain extent by injecting the test compound into the yolk sac, but the rate at which it is absorbed at this site is an unknown factor. Tests carried out in fertile eggs are therefore likely to overlook an active compound on account of defective absorption, or, because of non-specific inactivation of virus, to give false positive results. It is therefore not surprising to find that compounds which appear to have antiviral activity in eggs are almost invariably inactive when tested in mice. Takemoto and his coworkers found this to be the case, and the same fate has befallen many promising compounds studied by others.

The effect of the test compound on the growth of influenza virus in tissue culture is often studied. The rate of multiplication of the virus in test and control cultures is observed by removing samples of supernatant fluid at intervals and determining the amount of virus present by haemagglutination titrations. This method is widely used for antiviral screening, but also has theoretical defects. The content of virus in the supernatant fluid is a function not only of the extent to which virus has multiplied in the tissue but also of the extent to which the tissue cells have broken down (and thus liberated virus) under the artificial conditions of culture, assisted perhaps by a toxic action of the test compound, and of the extent to which the liberated virus has become inactivated by incubation at 37° C. for a prolonged period in the presence of an organic compound of unknown antiseptic potentialities. There are evident difficulties in attempts to solve the equation for the only variable in which we are interested—namely, the rate of growth of virus in the tissue in the presence and absence of the test compound. Influenza virus will also multiply in the lungs of mice after intranasal inoculation; the extent of virus multiplication can be assessed by the degree of pneumonic consolidation which is produced, and the method can be used for carrying out chemotherapy tests. Here again, however, the method is not free from objections, since the virus multiplies to maximum titre within the first day or so after inoculation, whereas lesions do not appear in the lungs until some days later, by which time much of the virus may have disappeared. Virus may also multiply in the lungs to a high titre without any lesions appearing at all. Thus the effect which is used for assessing the degree of virus multiplication is not directly related to it, and there is no reason why a compound which suppresses the lesions should be having any effect on the virus itself. The method is thus likely to give false positive results.

What of other viruses? Smallpox may well yield to the thiosemicarbazones. Measles must remain inaccessible to experiment until such time as the virus has been adapted with certainty to small laboratory animals. Yellow fever is kept under control by vaccination, and it is doubtful whether any laboratory is carrying out chemotherapy tests with the virus, although it can be handled easily. Poliomyelitis is the subject of much research, but here again progress is retarded by difficulties of method, not for theoretical reasons but because the only animals suitable for chemotherapy tests with the virus are the expensive and space-occupying primates or mice, and in mice the virus multiplies with an eccentricity of behaviour which is the despair of the statisticians. The common cold virus is not accessible to experiment, and success in this disease, as also with the others mentioned above, will probably come through empirical trials of compounds shown to possess activity against influenza or the pox viruses. Meanwhile, almost everything that the ingenuity of the organic chemist can produce is being tried out against viruses, and we may hope that ten years hence more satisfactory results will have been forthcoming.

## THE ARTIFICIAL KIDNEY

"There are numerous toxic states in which the kidneys are incapable of removing from the body at an adequate rate the natural or unnatural substances whose accumulation is detrimental to life." Written in 1913, this sentence from the opening paragraph of the first article on the artificial kidney[1] indicates the basis for the present-day use of the apparatus. Although clinical success was not achieved until the pioneer work of Kolff[2] in the past decade, sufficient experience has since been obtained to assess the value of the artificial kidney. Its principal uses lie in the treatment of acute renal insufficiency and in the removal of poisons, such as barbiturates, from the body.[3] Rarely it may have a place in the treatment of chronic renal failure.

In acute renal insufficiency due to post-operative renal shut-down, mismatched blood transfusion, or other causes of lower-nephron nephrosis when the renal lesion may be considered reversible, the artificial

[1] Abel, J. J., *et al.*, *Trans. Ass. Amer. Phys.*, 1913, **28**, 51.
[2] *New Ways of Treating Uraemia: The Artificial Kidney*. London. 1947.
[3] Merrill, J. P., *New Engl. J. Med.*, 1952, **246**, 17.
[4] *Lancet*, 1949, **2**, 229.
[5] Ibid., 1953, **2**, 791.
[6] *Ann. intern. Med.*, 1950, **33**, 100.
[7] *Arch. intern. Med.*, 1954, **93**, 61.
[8] Kyle, L. H., *et al.*, *J. clin. Invest.*, 1953, **32**, 364.

kidney has been used successfully to reduce the retention of nitrogen and potassium and to sustain the patient until renal function is restored spontaneously by the natural processes of repair. Owing largely to the work of Bull and his colleagues[4] in Britain it is now widely appreciated that serious degrees of nitrogen and potassium retention can often be avoided in the anuric patient by recognizing the condition early and treating the patient from the onset with a high-calorie, low-protein, potassium-free diet. Skilfully applied, this prophylactic treatment prevents the development of severe azotaemia and delays the onset of symptoms due to acute renal insufficiency. The patient may remain anuric but in good clinical condition until spontaneous renal recovery and diuresis start, usually before the sixteenth day. The diet used consists in an emulsion of arachis oil and glucose given by intragastric drip. If the patient is nauseated by this regime a satisfactory alternative is to infuse into the superior vena cava a 40% solution of glucose. If a dangerous degree of hyperkalaemia does develop despite this treatment—and it may particularly in obstetric patients, where sepsis and involution of the gravid uterus cause the release of large amounts of cellular nitrogen and potassium—ion-exchange resins can be used to remove the excess potassium. Milne and his colleagues[5] have employed this technique successfully in conjunction with the Bull–Borst diet. In cases of lower-nephron nephrosis where there has been delay in instituting treatment, and in cases with severe nitrogen or potassium retention despite adequate treatment, more radical measures may be required to remove the toxic substances from the body. The choice lies between the artificial kidney and intestinal or peritoneal dialysis. In expert hands excellent results have been obtained with the artificial kidney, but the apparatus—complex, costly, and difficult to handle—requires the constant attendance of a team of physicians, surgeons, and biochemists well versed in its use. Initially many centres employed the apparatus, but it became clear that treatment with it should be confined to a few special units where constant experience and high technical skill made its use a routine rather than a last heroic measure. At present its main exponents are Merrill in Boston, Hamburger and Mathe in Paris, and Alwall in Sweden. In Britain widespread understanding of Bull's work has meant that most artificial kidneys lie forgotten in the corner covered with a dust-sheet. If dialysis is required, the physician not constantly treating such cases will find intestinal or peritoneal dialysis an easier though admittedly a less effective method than the artificial kidney. Merrill[6] makes out a good case for using the artificial kidney as an adjunct to conservative medical treatment because "the amelioration of nausea and vomiting, and the increased well-being which accompany dialysis greatly facilitate medical management . . . and earlier mobilization of debilitated post-operative patients." This may well be so in the hands of an experienced team. The artificial kidney is contraindicated in the treatment of acute glomerulonephritis, for recovery from the acute phase is almost the rule, and in conditions complicated by peptic ulceration or any bleeding tendency because of the heparinization required.

Treatment with the artificial kidney in chronic renal failure is on less secure grounds. The patient with chronic renal disease may live for many years with a raised blood urea, which increases only slowly. An acute exacerbation of the underlying renal disease, whether pyelonephritis or glomerulonephritis, may produce acute superimposed on chronic renal failure, and here the artificial kidney can help, as in acute renal insufficiency, to tide the patient over the acute temporary phase. Dialysis has also been used successfully to prepare a patient with chronic renal failure for some surgical operation.[6] Recently Goldner and his associates[7] have reported the clinical response of chronic renal disease to dialysis with the artificial kidney. In 13 instances short symptomatic remissions of a few days were obtained, but on seven occasions longer remissions were seen, though the longest was only three and a half months. It seems unlikely that this treatment will commend itself to many or become established practice except in rare cases where a brief prolongation of life is imperative.

The artificial kidney is also of value in removing exogenously administered poisons from the body and has been applied successfully in the treatment of bromide, salicylate, and barbiturate intoxication. The first two of these can be satisfactorily treated by other means, but barbiturate poisoning remains a therapeutic problem, and excellent results have been reported with the artificial kidney.[8]

## ILLEGITIMACY AND THE WAR

If the series of volumes in the official history edited by Sir Keith Hancock is now beginning to unravel the tangled administrative history of the second world war for us, its social consequences still remain much of a mystery, despite all the efforts of the historians. The most recent volume in this series, *Studies in the Social Services*, contains a most interesting account of the problem of illegitimacy and the official policies designed to deal with it. But, when all is said and done, the impression given is of a number of well-meaning attempts to remedy situations which were often some-

what alarming, never more than partially understood, and always associated with endless suffering, much of it avoidable. We are left in the dark so far as the origins of the problem itself are concerned.

The crude facts still constitute much of a mystery for us. It is only too easy to say that "young women are to be expected to kick the traces over" during the social upheavals of a bitterly contested war. But the truth is that they did nothing of the kind. The astonishing fact is that among mothers under the age of 25 the percentage of illegitimate births during the whole war was actually lower than in 1938–9. The chief problem lay with the women between 25 and 30 years of age; those between 30 and 35 were almost as worrying, but why this is so nobody seems to have the least idea. The authors of *Studies in the Social Services* suggest that this phenomenon may be associated with a general rise in the proportion of first births to older women, or with the greater knowledge of birth control techniques on the part of younger women, or with the fact that the maximum rise took place in the group who had been children during the first world war. But all this is unfortunately mere speculation, and it is obviously a promising field for research.

When war broke out the attitude of Whitehall to the problem of the unmarried mother was based on the principle of "equal rights for all mothers." The Ministry of Health "allowed no discrimination against unmarried women, but it was equally opposed to granting them favours." Needless to say, its refusal to recognize the fact that the needs of the unmarried mother are in many respects much greater than those of her married sister could not be maintained in the face of the day-to-day emergencies of practical administration. Unmarried mothers who took advantage of the evacuation scheme (often in a very literal sense), those who were war workers required to live away from home, and unmarried mothers in the Services all had to be cared for in the end under special schemes. Endless muddle and inefficiency resulted. The maternity services were, in any event, gravely overburdened by the conditions with which they had to deal, quite apart from the problem of illegitimacy. Even in 1945, when the war in Europe was over, pregnant women were still registering for evacuation to obtain the maternity beds that were not available in their own areas. There was a high proportion of unmarried women among them, and the administrative conflicts that resulted between the authorities in the reception areas and those in the towns from which they came were as hard fought as might be expected. Muddle, ignorance, and sometimes perhaps indifference were tempered by the human sympathy that broke through at times, particularly so far as the unmarried Service woman was concerned. As illegitimacy is a problem that no public authority (or citizen) likes to face squarely, voluntary associations and public-spirited individuals had to deal with it to the best of their ability, but with very slender resources at their command. In the end, however, a great deal of administrative tidying up was done by the Ministry of Health in collaboration with the National Council for the Unmarried Mother and her Child. A scheme of co-operation was worked out between the welfare authorities and the voluntary associations, and it was embodied in a circular issued by the Ministry of Health in 1943. This has remained the basis of Government policy ever since.

Nevertheless, the plain statement recorded in this volume is that "for about four years of war, illegitimacy, as a social problem, was not regarded as a responsibility of Government, and there was no general policy to deal with it." Only too often it was simply ignored, as when hostels for young women munition workers were built immediately opposite large military establishments—despite the strong opposition of the regional medical officers. In general, the reading of the account presented to us leaves one with unpleasant memories of the sufferings of individual women. But, for all that, it closes on a more optimistic note, recording that "it was one of the social consequences of the war that the Government accepted new responsibilities for the welfare of unmarried mothers and their babies."

## CANCER OF THE PANCREAS

It is only within the past twenty years or so that a surgical technique has been evolved for the wide resection of cancer of the pancreas and of the terminal part of the bile ducts. But, despite a most encouraging improvement both in the safety of the procedure and in the number of patients to whom it can reasonably be offered, the results of the operation, as measured by the number cured of the disease, have been disappointing. It is true, however, that for the patient whose tumour is detected early surgery has a great deal to offer both in the relief of symptoms and in the prolongation of life: the problem of cancer here, as at so many other sites, is early diagnosis.

Some of the delays in diagnosis are no doubt attributable to the relative inaccessibility of the pancreas, whether defined by anatomy, by radiology, or even by biochemistry. But too often delay is due to a widely held misconception of the significance of the early symptoms of pancreatic cancer. Professor Charles Rob and Mr. Rodney Smith, in an article appearing at p. 330 of the *Journal* this week, draw attention to the misleading teaching on this subject which seems still to be current. Their study is based on an analysis of the case histories of 190 patients who have passed under their care. The first truth which their analysis reveals is the importance of pain as a first symptom. Whatever the site of the cancer, pain is the first complaint in 56.8% of cases. The distribution and character of the pain may give a clue to the site of the tumour. When it is in the head of the pancreas, the pain is typically in the epigastrium and may suggest the presence of a peptic ulcer or of gall-stones. In contrast, when the tumour is in the body or tail, the pain radiates from the epigastrium round into the back, and, being aggravated by the recumbent position, it is particularly distressing

[1] *Diseases of the Pancreas and their Treatment.* Philadelphia. 1902.
[2] Arkin, A., and Weisberg, S. W., *Gastroenterology*, 1949, **13**, 118.
[3] Millar, T. M., *Edinb. med. J.* (*Trans. med. chir. Soc. Edinb.*), 1951, **58**, 1
[4] Broadbent, T. R., and Kerman, H. D., *Gastroenterology*, 1951, **17**, 163

at night. Considerations of anatomy make it easy to understand why jaundice is always a late feature in cancer of the body or tail, but it is more surprising to learn that pain is as often a first symptom as jaundice when the neoplasm is in the head or in the ampulla. The not uncommon teaching that painless and progressively deepening jaundice is the most striking feature of cancer of the pancreas is no longer acceptable. Most surgeons interested in the problems of biliary disease can recall from their own experience puzzling fluctuations and even complete remissions of jaundice which were shown at operation to be due to obstruction by an infiltrating cancer.

In a minority of patients vomiting is a first symptom, the clinical picture resembling pyloric stenosis only in the cases where the vomitus does not contain bile. Bleeding from an ampullary cancer results in a positive occult blood test in a high proportion of cases, and if long continued will lead to a profound anaemia. Every undergraduate can enunciate Courvoisier's law, admittedly with wide variation in accuracy. It is surprising that Rob and Smith felt the gall-bladder clinically in just over half of the jaundiced patients, though the validity of the law is thereby in no way questioned. In the remainder it was effectually concealed by an associated hepatic enlargement. When a pancreatic neoplasm is palpable it is in almost every instance inoperable. As Rob and Smith acknowledge in their text, the importance of pain as a symptom of pancreatic cancer was emphasized by those two great pioneers of abdominal surgery, Mayo-Robson and Berkeley Moynihan,[1] more than 50 years ago. Though this teaching has been further underlined on many occasions in surgical writings during the past ten years,[2–4] it does not seem yet to have become fully incorporated into our standard textbooks of surgery: it is high time that it did.

## CONTACT LENSES

On theoretical grounds axial ametropia can best be remedied by a correcting lens placed within the eye at its nodal point, located in the posterior portion of the crystalline lens. The introduction of Ridley's intraocular acrylic lenticulus[1 2 3] meets this requirement, but is applicable only to the problem of aphakia, and only to certain cases in that category. Lenses placed in immediate contact with the anterior surface of the cornea are 7 mm. in front of the nodal point of the eye and thus deal almost as effectively with the axial component of ametropia, while having the further advantage of replacing the often irregular cornea–air interface with a smooth lens–air interface of the same refractive index. Lenses placed at spectacle distance (20–22 mm. in front of the nodal point) are obviously the most convenient means of correcting refractive errors, but optically they are less satisfactory, particularly where the error is large and irregular or anisometropia is marked.

The large amount of work expended on improving the haptics of contact lenses is therefore understandable. Early types of lens which depended for success upon a very close and accurate fit were impeded by the phenomenon of veiling first described by Sattler[4] in 1938. This is caused by corneal oedema, the mechanism of its formation being obscure, but it may be due to interference with the respiration of the corneal epithelium. Veiling can be relieved by providing the lens with one or more perforations which permit ventilation of the anterior corneal surface.[5] A recent survey by Choyce[6] of a large series of ventilated glass contact lenses showed that the results were significantly better than with similar unventilated lenses. It is probable that the same would hold true of plastic lenses. The introduction of the ventilated lens thus represents an advance in the haptics of contact lenses. Such lenses may be made of either glass or plastic ; the former are the more expensive, since they are more difficult to work and require more fittings. Plastic lenses, although needing fewer fittings and being thus cheaper to produce, are more readily scratched and deformed by heat, either accidental or climatic. In general, contact-lens practitioners either prefer glass lenses and will hear no good of the plastic variety or take the exactly opposite view—a situation which accounts for the impossibility of obtaining reliable statistics which relate the performances of the two types. It is thus not possible to declare with certainty which is the better type ; one patient may be better suited to a glass lens and another to a plastic lens, and if failure is apparent with one variety it is wise to try the other. Whichever material is used, a contact lens represents a large foreign body in the conjunctival sac, and initial discomfort is common. With patience and perseverance on the part of the subject and fitter remarkable tolerance is often acquired. The best stimulus to persistence with the fittings comes from real visual need, and excellent results are often obtained in high myopia, high degrees of compound myopic astigmatism, irregular astigmatism, and keratoconus. The lenses are of limited use in other refractive conditions such as low myopia and aphakia. Certain people much in the public eye, such as politicians and members of the theatrical profession, find them a help ; but unfortunately contact lenses are rarely comfortable in hot, stuffy, smoky, or crowded surroundings, just when they would be of most service.

For the ophthalmologist contact lenses are a notable aid in certain diagnostic research procedures, such as gonioscopy, fundus examination, and *x*-ray location of foreign bodies. They may help in the management of cases where corneal protection is required, as in lagophthalmos, entropion and trichiasis, and neuroparalytic keratitis ; and they can also be of use in preventing the formation of symblephara following burns of the conjunctival sac, and in degenerative conditions such as mustard-gas keratitis and recurrent erosions. The fitting of contact lenses is not without its dangers, and all contact-lens wearers should pay regular visits to their ophthalmic surgeon during the fitting period and after the lenses are in regular use. The growth of contact-lens centres presided over by non-medical staff is a disquieting feature of some better-known shopping centres, and the profession has a duty to draw the attention of the general public to the unwisdom of placing their eyes in the charge of these practitioners in centres where no medical control is exercised.

[1] *Lancet*, 1952, **1**, 118.
[2] *Brit. J. Ophthal.*, 1952, **36**, 113.
[3] Ibid., 1954, **38**, 156.
[4] *Klin. Mbl. Augenheilk.*, 1938, **100**, 172.
[5] Dallos, J., *Brit. J. Ophthal.*, 1946, **30**, 607.
[6] Ibid., 1954, **38**, 100.

# RADIOISOTOPES IN MEDICINE

[BY A SPECIAL CORRESPONDENT]

The second Radioisotope Conference, sponsored by the Atomic Energy Research Establishment, took place at Oxford from July 19 to 23. The scientific communications covered a very wide range of topics in the biological and physical sciences. In the sessions devoted to biological science there were 45 papers occupying the first three days of the Conference.

## Therapy

Several groups of workers reported developments in the use of radioisotopes for the treatment of malignant disease. The papers in this section dealt with examples of each of the three principles used in radioisotope therapy: internal administration of the isotope in some chemical form which is concentrated selectively at the site of the tumour; intravascular injection of radioactive particles which are trapped in the capillaries of the organ containing the tumour; and local application of the radioisotope in or near the tumour.

Most of us have learnt by now not to hope for anything spectacular from these methods of treatment; nevertheless, with further advances in technique, we may expect to see a steady improvement in the prognosis of many types of malignant disease not amenable to conventional radiotherapy. One of the difficulties in treating patients by internally administered radioisotopes is to predict the quantity of isotope necessary to influence the tumour tissue without giving too much radiation to the rest of the body. Dr. E. C. EASSON and his colleagues discussed this problem in connexion with $P^{32}$ in the treatment of myeloid leukaemia. They showed that the fall in the white blood cell count after a single dose of $P^{32}$ provides a good indication of the total dose the patient will need.

Another way of achieving better therapeutic results with radioisotopes lies in the choice of an isotope having more suitable radiation characteristics or greater selective concentration in the tumour tissue. To this end Dr. J. G. HAMILTON and his colleagues at Berkeley, California, have studied the metabolism of the radioactive halogen astatine-211 in rats and humans. They have shown that this element is concentrated in the thyroid, though probably not to the same extent as iodine, and that, like radioactive iodine, it can be used to destroy selectively the thyroids of dogs and monkeys. Since astatine decays by emission of alpha particles, which have a range of less than 70 $\mu$ in soft tissue, the radiation damage does not extend beyond the site of concentration. This would certainly be a favourable factor in the treatment of malignant or non-malignant thyroid disease. However, the rate of decay of astatine-211 (half period = 7 hours) is so high that the blood would normally receive an unduly large amount of radiation before the dose had had time to accumulate in the thyroid tissue. On the evidence presented by Dr. Hamilton's group astatine-211 does not appear to be potentially a better therapeutic agent than $I^{131}$, but it might be worth trying out in those patients with thyroid cancer in whom the metastases concentrate iodine and then discharge it very rapidly.

Dr. E. E. POCHIN and his colleagues described their experience with J. H. Muller's technique for the intravenous injection of radioactive gold on carbon particles. If the particles are more than about 30 $\mu$ in diameter they are held up in the lung capillaries, where they irradiate the lungs selectively. If the particles are injected by catheter into one pulmonary artery, the irradiation can be restricted mainly to a single lung. By measuring the radioactivity over different parts of the patient after an injection of radiogold, Dr. Pochin's group were able to map out the distribution of the particles throughout the body. On the basis of these measurements they calculated the total radiation given to the lungs, liver, and other tissues when known amounts of radiogold are injected. Their results showed that it would certainly be worth while trying to improve this technique by using other isotopes with shorter decay rates and less intense gamma-ray emission.

Dr. R. C. TUDWAY and others described an ingenious method for irradiating the cervix uteri by applications of iridium-129, without excessive irradiation to near-by organs in the pelvis. Dr. F. CRAINZ, from Catania, Italy, described a method for destroying the uterine endometrium without affecting ovarian function. The basis of this method consists in the local application of yttrium-90, a beta-ray emitter, in thin-walled metal tubes. Other papers in this field dealt with the treatment of bladder papillomas by means of colloidal radiogold solutions introduced into the bladder; the possible uses of radioactive bismuth either administered internally or as a substitute for radium; the fate of yttrium-90 when injected into body cavities; and the metabolic fate of injected "synkavit" labelled with radioactive bromine.

## Diagnosis

One of the most valuable uses of radioisotopes in medicine has been in the development of diagnostic tests. Several of the papers revealed a continued interest in this field. Professor J. ROTBLAT and Dr. G. M. OWEN gave a simplified analysis of the various phases of the metabolic cycle of radioiodine in patients with diseases of the thyroid, including a few with iodine-concentrating carcinomas. In this small series they found that thyroid carcinomas tended to discharge a test dose of $I^{131}$ much more rapidly than normal thyroid tissue, and they suggested that this might be helpful in distinguishing between normal and malignant thyroids. However, a rapid rate of turnover is by no means always found in cancer of the thyroid, and it seems rather unlikely that a test of this sort would be of much value by comparison with the standard clinical methods.

Dr. H. C. ALLEN described an apparatus for outlining extended sources of radioiodine-131 in the body. This method has been developed by Dr. Allen and his colleagues at Houston, Texas. They were able to obtain a beautifully sharp outline of the source by using a collimated scintillation counter, combined with a device for cutting out the pulses arising from radiations scattered laterally from the source. The counter is moved up and down the surface of the body over the source of radiations, and the response printed automatically as a silhouette or "gammagram" of the region in which the radioiodine is concentrated. This type of apparatus is now widely used in the United States for locating brain tumours and for outlining functioning thyroid tissue in the neck and in abnormal situations. At present these machines are very expensive to build, but many hospital physics departments in this country should be able to afford a simplified type such as that mentioned by Dr. E. W. PULSFORD from the Atomic Energy Research Establishment at Harwell.

Dr. H. G. THODE described the work done by his group at Toronto on the concentration of iodide in the saliva. They found that the secretion of radioiodine in the saliva after a test dose is diminished in Graves's disease and after injections of thyrotrophic hormone. From these and other findings Dr. Thode concluded that the functional activity of the salivary glands is inversely related to that of the thyroid, and that the salivary glands play an important part in regulating the amount of thyroid hormone circulating in the body. However, the facts presented by Dr. Thode did not warrant this conclusion. If two organs compete for a given quantity of a substance and one of the organs is stimulated to take more, unless some new factor intervenes the other is bound to get less. Some such simple mechanism based on competition appears to be the most likely explanation for their findings. Dr. Thode and his group have used the salivary secretion of a dose of radioiodine as a diagnostic test of thyroid function. It remains to be seen whether this is preferable to the many other radioiodine tests of thyroid function already in use.

During the past few years a good deal of clinical work with radioactive iron has been done in the United States. $Fe^{59}$ emits high-energy gamma radiations detectable by an external counter, and is clearly of great potential value in the study of diseases of iron metabolism; but until recently $Fe^{59}$ of a suitable activity has not been available in Britain. Now, however, it can be obtained from Harwell with a specific activity of at least one microcurie per microgram, and several groups of British workers have already begun to take advantage of this. Drs. E. M. LEDLIE and C. F. BAXTER described their technique for following the metabolism of a test dose of radioiron in patients with disorders of the blood-forming organs, and showed how these disorders may be traced to particular phases in the metabolic cycle of iron. Like Hennessey and Huff at Berkeley, they obtained evidence that the spleen may make red blood cells when marrow function is depressed.

Another useful clinical application of a radioisotope was described by Dr. N. VEALL and his colleagues. These workers have developed a method for measuring the cardiac output in humans. The principle is the same as that used in the dye dilution method, in which the cardiac output is estimated from the rate of change of concentration of a dye in the arterial blood immediately after an intravenous injection. But in this case the material injected is human plasma albumin labelled with radioiodine, and its concentration in the heart is followed by means of a counter placed directly over the base of the heart. The external counting rate can be related to the concentration of the labelled albumin in the blood by taking a single venous blood sample when the test dose has mixed completely in the blood. The method is simple to carry out and could be used for serial estimations of the cardiac output if the plasma were labelled by a very short-lived radioisotope.

A useful test for the viability of stored human skin, depending upon the uptake of $P^{32}$ *in vitro*, was described by Dr. W. GEMMEL and his colleagues.

## Physiology

There were several papers on physiological subjects. Dr. H. MILLER and his group from Sheffield described their attempts to measure the rate of exchange of the plasma sodium with sodium in the bone. Using a long-lived gamma-ray-emitting isotope of sodium ($Na^{22}$), they were able to estimate roughly the rate at which radioactive sodium enters the bone in the knee-joint. Their evidence suggests that mixing of the plasma sodium with bone sodium may take several days for completion. This raises the interesting possibility that bone may contain a reservoir of sodium on which the body may draw in emergency. Nothing appears to be known about the chemical form of this slowly exchangeable fraction of the body sodium.

Using $Na^{24}$, a short-lived isotope of sodium, Dr. P. BENDA and his colleagues at Villejuif have studied the movement of Na across the blood-brain barrier. By measuring the rate of transfer of labelled sodium from the blood to the cerebrospinal fluid in normal and pathological conditions they showed that the most active transfer occurs through the choroid plexus, but that there is also some direct transfer into the lumbar C.S.F. Other papers in this section included one by Drs. G. W. REED and A. D. CARE on the electrolyte imbalance which often follows anastomotic operations to the bladder or ureters, and one by Dr. S. ROWLANDS and his colleagues on the circulatory effects of haemorrhagic shock. Using two different radioactive agents for labelling the red blood cells, these workers obtained evidence that after the removal of a large fraction of the total blood volume some of the remaining blood ceases to be in active circulation. Dr. D. N. WALDER has studied the blood flow through muscles in humans. His results suggest that alterations in the blood flow during exercise, as measured by the rate at which a local injection of radiosodium disappears, may give useful information about the state of the peripheral blood vessels.

## Intermediary Metabolism

The study of intermediary metabolism has advanced considerably since the advent of radioisotope techniques. In many cases it has been possible to elucidate the detailed steps by which a complicated molecule is built up and broken down by the organism. From this work there have emerged several facts of general interest. It has been found, for instance, that the animal body tends to use a limited variety of very simple precursors for the synthesis of large and complex molecules such as cholesterol, glycogen, and the haem pigments. Studies with labelled precursors of organic compounds have also shown that enzymes can distinguish between different forms of apparently similar labelled molecules.

Drs. P. SCHAMBYE from Copenhagen and H. G. WOOD from Cleveland described an interesting example of this type of isomerism which occurs in the synthesis of the glucose units of glycogen from labelled glycerol. If rats are given acetate in which the carboxyl carbon atom is labelled with $C^{14}$, the label appears predominantly in the two middle carbon atoms of glucose (atoms 3 and 4). The labelled glucose can then be degraded to glycerol ($CH_2OH.CHOH.CH_2OH$) in which the molecules are labelled only at one end. Now glycerol, according to classical standards, is a symmetrical molecule. When, therefore, two molecules of this labelled glycerol unite to form the six-carbon-atom unit of glucose, both ends of the glycerol should have an equal chance of joining together, and we should expect to get glucose labelled equally in the four positions marked with a star: $\overset{*}{C}\text{-}C\text{-}\overset{*}{C}\text{-}\overset{*}{C}\text{-}C\text{-}\overset{*}{C}$ (1 2 3 4 5 6). Surprisingly, however, this does not happen. When the labelled glycerol is incubated with liver slices, and each carbon atom of the newly formed glucose isolated separately, the label is found only on carbon atoms 3 and 4. This must mean that an enzyme concerned in the biosynthesis of glucose units can distinguish one end of the glycerol molecule from the other. This is only one example of a type of problem which could never have been attacked without the use of an isotopic label.

The metabolism of the plasma proteins has been investigated in many laboratories by means of isotopic labelling techniques, and we now know that plasma proteins are constantly being broken down and resynthesized. In one type of investigation a sample of the plasma protein, labelled *in vitro* by radioiodine, is injected intravenously, and the rate of fall of radioactivity in the blood is then measured. In other experiments a labelled amino-acid is given by mouth, and the amount of the label in the various plasma protein fractions is then measured over a suitable period. The great disadvantage of the first method is that most of the techniques used for labelling proteins *in vitro* undoubtedly lead to some denaturation of the proteins. For this reason, much of the published work on the rate of degradation of plasma proteins *in vivo* is of little value. The second method does not suffer from this drawback, because the labelled proteins are made by a biosynthesis. On the other hand, the results are difficult to interpret, because, at least during the early part of an experiment, synthesis and breakdown of labelled protein may occur at the same time. Both these disadvantages have been overcome by Dr. A. DOVEY and his colleagues at Mill Hill. They gave a mixture of highly radioactive $C^{14}$-labelled amino-acids to a rabbit, and then they removed the plasma after an interval sufficient to permit the synthesis of the maximum amount of labelled plasma protein from the amino-acid mixture. The naturally labelled protein could then be injected into other rabbits and the rate of metabolic breakdown of the different plasma protein fractions measured in the recipients by following the gradual fall in radioactivity. In contrast to what has been found by other workers, they found that, with the exception of fibrinogen, all the plasma protein fractions studied were broken down at the same proportional rate. This suggests that the body gets rid of a fixed volume of

plasma each day, perhaps by some simple process such as phagocytosis.

There were several other interesting papers dealing with the metabolism of a wide variety of substances. Professor A. C. FRAZER and his colleagues have developed methods for measuring the rate at which small amounts of a foreign substance are eliminated from the body. Dr. J. ROCHE and his colleagues from Paris have identified some of the products of thyroxine and tri-iodothyronine metabolism which are excreted in the bile and urine. (Tri-iodothyronine is thyroxine less one iodine atom.) They have confirmed the finding of Taurog and others that both these compounds are converted to their respective glucuronide by the liver. Dr. A. E. ALMOND and his colleagues have studied the fate of labelled antigenic proteins injected intravenously into rabbits, and Dr. H. R. V. ARNSTEIN and others have studied the biosynthesis of penicillin from $C^{14}$ and $S^{35}$-labelled precursors. Dr. P. LACROIX from Louvain described his work on the uptake of labelled sulphate by the bones of adult animals. Using the technique of autoradiography, he showed that the sulphate accumulates in regions where osteogenesis occurs and that sulphate metabolism in bone is probably concerned in the formation of the mucopolysaccharides of the bone matrix.

Dr. C. ROSENBLUM and his colleagues from New York have prepared vitamin $B_{12}$ labelled with cobalt-60 having a high specific activity. With this material they have developed a method of testing for the effectiveness of preparations of intrinsic factor. This depends upon their finding that the urinary excretion of a test dose of vitamin $B_{12}$ by patients with pernicious anaemia, either in relapse or in remission, is increased by feeding intrinsic factor of known potency. When assessing the potency of a sample of intrinsic factor it is, of course, no longer necessary to rely upon the clinical response of patients with pernicious anaemia in relapse. However, Dr. Rosenblum's test may have some advantages over the test in current use, based on the faecal excretion of radioactive vitamin $B_{12}$.

### New Syntheses

For the study of intermediary metabolism it is often necessary to synthesize complex labelled molecules, and this may involve the development of new techniques. Several new syntheses, or improvements on old methods, were reported at the Conference. Dr. J. R. CATCH from the Radiochemical Centre at Amersham has developed a technique for the mass production of $C^{14}$-labelled amino-acids of high specific activity. The labelled amino-acids are obtained by hydrolysing the proteins of algal cultures grown in an atmosphere containing $C^{14}O_2$. The amino-acids obtained by this method are labelled more or less uniformly, so that they are not suitable for experiments in which the label must be confined to a particular atom in the carbon skeleton. However, they are likely to be of great value in many problems of intermediary metabolism. Samples prepared by Dr. Catch were used by Dr. A. Dovey and others in their study of plasma protein metabolism.

Dr. P. AVIVI and others described a method for preparing tritium- and $C^{14}$- labelled organic compounds of high specific activity, and they explained how these compounds can be used to estimate small amounts of natural substances by the method of isotope dilution. Dr. GEORGE WOLF and his colleagues from Urbana, Illinois, described a new synthesis of radioactive vitamin A, and Drs. A. CRITCHLOW and M. K. GOLDFINCH described their method for preparing radioactive thyroxine of high specific activity and free from labelled tri-iodothyronine. Dr. R. F. GLASCOCK described methods for the preparation of several tritium-labelled compounds, including stearic acid and hexoestrol. Several new syntheses of labelled compounds were also reported by Dr. L. PICHAT and others from the laboratories of the French Atomic Energy Commission. Among the more interesting of these syntheses was a method for preparing isoniazid labelled in the ring.

### Radiobiology

The number of papers devoted to radiobiology was disappointingly small, although the standard was uniformly high. The effects of whole body irradiation on the metabolism of radioiron in rats were described by Dr. L. F. LAMERTON and his colleagues, and studies on the uptake of labelled glycine by the Ehrlich ascites tumour were reported by Dr. A. FORSSBERG and Dr. G. KLEIN from Stockholm. Dr. L. EHRENBERG and his colleagues, also from Stockholm, gave an interesting paper on the use of a large outdoor gamma-ray source of cobalt-60. This was used to study the effects of radiations on the growth, fertility, and mutation rate of crops cultivated under natural conditions.

### Conclusion

Finally, the organizers are to be congratulated on the smooth running of the Conference and on the arrangements made for exhibiting commercially available apparatus. However, in retrospect one may question the wisdom of bringing together several hundred scientists to discuss so wide and varied a selection of topics. Radioisotopes have by now reached the stage at which they are used routinely in almost every laboratory, and techniques based upon their use are rapidly ceasing to determine the type of problem a research worker wishes to investigate. For this reason, the mere fact that workers in widely separated fields may all happen to use radioisotopes no longer constitutes a distinctive common interest. This may account for the lack of vigorous discussion after many of the papers. If there is to be another Radioisotope Conference, perhaps it would be better to restrict it to a limited field, such as Radioisotope Therapy, in which progress still depends to a large extent upon technical advances.

# Nova et Vetera

## ALEXANDER OGSTON—BACTERIOLOGIST

Early in the history of bacteriology those Gram-positive cocci commonly found in acute suppurative lesions were designated "staphylococci" and by that name have been familiar to several generations of medical men. In the last edition of Bergey's *Manual of Determinative Bacteriology* (1948) the genus *Micrococcus* now includes those organisms formerly in the genus *Staphylococcus*. This banishing of the genus *Staphylococcus* has not passed unnoticed. Some British workers have recently countered this attempted change in bacterial nomenclature by suggesting that the genus *Staphylococcus* should embrace all aerobic micrococci. The outcome of this taxonomic debate is as yet undecided, but there is much to be said for retaining the term "staphylococcus," which is so closely associated with the name of Alexander Ogston, one of the earliest workers in this field.

Ogston, who was born in Aberdeen in 1844, was a distinguished surgeon and held the regius chair of surgery in Aberdeen from 1882 till his retirement in 1909. He had many interests in medicine, and not the least of these was the causation of suppuration, in the study of which he was conspicuously successful. He has recorded in some autobiographical writings:

> "Often I meditated on the subject [acute suppuration] and became the more convinced that there was a single cause, and that the cause was some special germ. But it was some time before it was possible for me to verify this conviction. At length I came upon a case of disease which promised to solve the problem."

This was a case of extensive suppuration of the leg, from which he evacuated some of the material through the unbroken skin. He stained the pus with aniline violet and examined it under an ordinary student's microscope. Among

the pus cells and debris tangles, tufts, and chains of organisms stood out distinctly. This finding suggested to Ogston the possible solution to a great problem, which he immediately set about to unravel.

### B.M.A. Scholarship

In 1878 Koch had published his monograph *Untersuchungen über die Aetiologie der Wundinfektionskrankheiten* (English translation, *The Etiology of the Traumatic Infective Diseases*, in 1880), in which he showed that the injection of putrefying substances such as blood and meat infusion into mice and rabbits could cause a number of different infective diseases such as septicaemia, abscesses, and erysipelas. In the preface he stated :

"The object of the enquiry was to determine whether the infective diseases of wounds are of parasitic origin or not. Owing to extraneous circumstances I found it necessary to confine myself solely to experiments on the action of putrid materials on animals. . . . In order to obtain a complete answer to the question it would have been necessary to carry out a further series of experiments on animals with materials obtained from persons suffering from or who had died of traumatic infective diseases and, what indeed seems to me to be the most important, to look for micro-organisms in the human body."

It was Ogston who filled in this gap in our knowledge using some of the newer methods of investigation described by Koch in his monograph. He had a laboratory built behind his house, obtained a Home Office licence for animal experiments, and applied to the British Medical Association for help to finance his research work. From the Minutes of the Scientific Grants Committee of the B.M.A. the following extract is significant[1]:

"August 6, 1879.

"It was resolved that it be recommended that the following grant be made:

"Dr. Ogston: For a research into the Relation between Bacteria and Surgical Disease. £50."

The apparatus bought by Ogston with his money included a Zeiss microscope with Abbe condenser and oil immersion lens, a camera, and a zinc incubator. In August, 1880, a further grant of £10 was made towards a continuation of this research.

Ogston presented the results of his investigations to the Congress of German Surgeons meeting in Berlin on April 9, 1880, as "Über Abscesse." In the following year, 1881, his paper "Report upon Micro-organisms in Surgical Diseases" was published in the *British Medical Journal* of March 12.[1] This described the examination of 82 abscesses, of which 13 were chronic "cold" abscesses, 4 chronic, and the remaining 65 acute abscesses of only a few days' duration. In these latter he found micrococci, sometimes appearing as chains, sometimes as clusters, and at other times as a mixture of chains and clusters. He cultured them, often with extreme difficulty, and introduced fresh hens' eggs as a culture medium. Injection of pus containing these micrococci into mice produced abscesses and sometimes death of the animal, and the cocci injected were found to have multiplied. Pus heated or treated with phenol was found to have lost its disease-producing property.

It is interesting to note that at approximately the same time as Ogston was carrying out his systematic investigation of abscesses Pasteur was examining pus from furuncles. He found in them cocci, which he cultured on chicken muscle broth and yeast broth, and on inoculation of these cocci was able to produce abscesses in rabbits and guinea-pigs. Pasteur's results were communicated to the Academy of Sciences on May 3, 1880.

### Clusters of Micrococci

In a later paper, "Micrococcus Poisoning,"[2,3] Ogston distinguished the micrococci which appeared in chains, already designated "streptococci" by Billroth, from the other micrococci which were seen as masses or clusters. To these latter he gave the name of "staphylococci" at the suggestion of the professor of Greek at Aberdeen University, W. D. Geddes.

Ogston was knighted in 1912 and in 1914–15 was President of the B.M.A. He died in Aberdeen on February 1, 1929, only twenty-five years ago, but by that time his contribution to bacteriology, begun fifty years before, had been established beyond doubt. In these days when money given for research is measured in thousands of pounds the grant of £60 which Ogston received seems small, but there have been few pieces of work where the results were so rewarding for so small an outlay.

I. A. PORTER.

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# Reports of Societies

## CONFERENCE ON FERTILITY

### Results from Fertility Clinics

At the annual conference of the Society for the Study of Fertility held on July 22 and 23 in London, Miss DOROTHY M. SHOTTON (Birmingham) reviewed a series of 2,000 patients who had attended her fertility clinic since 1944. Of these, 25% had become pregnant. Of the 472 women with primary infertility who had conceived, 61% underwent a normal confinement, 9.3% aborted, and 0.8% had ectopic gestations. There were 16.5% of forceps deliveries and 9.3% of caesarean sections. Perinatal mortality was 4.4% and there was no maternal mortality. There were only 5 congenital malformations, 3 being stillborn. On the whole, the outcome had been remarkably good and obstetric complications few. Other speakers expressed surprise at the low abortion rate, with which they contrasted their own experiences, usually of the order of 20 to 25%.

Dr. MARGARET JACKSON (Exeter) gave a preliminary report of a large-scale follow-up of infertility patients, drawn from a total of some 2,600 couples whom she had seen over the past 20 years. One feature which had so far emerged was that considerably fewer of the patients with primary sterility conceived without assistance than did those with secondary sterility.

Dr. MARY POLLOCK (London) described her experience with sodium acetozoate in 30% aqueous solution as a medium for hysterosalpingography. It had proved a satisfactory contrast medium, which gave rapid results and showed up mucosal detail better than more viscous substances. Normally, all was absorbed within 30 minutes. No ill effects had been observed, but she did not think it was superior to diodone.

### Artificial Insemination

Dr. E. J. FARRIS (Philadelphia) gave details relating to 100 women who conceived following donor insemination timed on the basis of his now well-known rat ovary hyperaemia test for the prediction of the time of ovulation. Each woman received only one insemination in any cycle, and, of the 326 inseminations required to achieve the 100 conceptions, only 37 of the 226 failures remained unexplained. In some cases, it appeared that insemination had to be not within days but literally within hours of the apparent time of ovulation. Most of the conceptions occurred on cycle day 12. There were 31% of abortions in this series, and 1 tubal pregnancy, in a woman who had previously had plastic surgery of the tubes.

Dr. RAOUL PALMER (Paris) discussed the techniques and value of coelioscopy in sterility problems, with due emphasis

of the possible dangers in unskilled hands. Abdominal coelioscopy afforded a better general view of the pelvic viscera than could be obtained by the vaginal approach, but the latter was easier to perform and somewhat safer than the former. There were, however, indications and contraindications for both, so that they were not strictly alternatives. Dr. Palmer illustrated and described the coelioscopic findings in a large number of pathological conditions. He felt that many useless laparotomies for attempted operations on the Fallopian tubes could be avoided by preliminary coelioscopy.

### Adrenal Hyperplasia

Dr. G. E. SEEGAR JONES (Baltimore) discussed four groups of patients with congenital adrenal hyperplasia : (1) female pseudohermaphrodites, (2) post-natal virilism due to adrenal hyperplasia, (3) post-puberal hirsutism, infertility, and oligomenorrhoea with elevated 17-ketosteroid excretion, and (4) as in (3) but with normal 17-ketosteroid excretion. Examination of the enlarged adrenals from 15 patients in groups 1 and 2 showed hyperplasia of the reticular zones with lack of the fasciculata zone. In normal adrenals the latter zone contains birefringent lipids and the former does not, but in these hyperplastic adrenals the distribution was reversed. It is the fasciculata that produces the glucocorticoid type of hormone, so that absence or functional incompetence of the fasciculata zone was the cause of the disturbed hormonal pattern. Failure adequately to convert steroid precursors into glucocorticoids left the pituitary uninhibited ; in consequence, A.C.T.H. was secreted in excess, causing the adrenal overactivity, with the production of aberrant, androgenic steroids of which pregnanetriol might be the most important. The condition could be corrected by administration of cortisone. With a daily dose of 50 mg. orally for the first month, followed by 25 mg. daily subsequently, ovulation was induced in all of 16 patients in group 3, and 3 out of 10 conceived ; of group 4 patients 14 out of 15 ovulated, and to date all but 4 out of 11 had conceived.

### Subfertility in the Male

Dr. R. IRVING-BELL (Bristol) spoke of his observations on the routine physical examination of 1,200 men seen at a male subfertility clinic. He found that anthropometric measurements bore no relationship to infertility except in cases with gross endocrine disorder. In a comparison of 175 men whose semen quality was good with 108 men who showed azoospermia or extreme oligospermia, few striking differences emerged. Abnormalities of the testicle were seen in only 1.5% of the former group, but in 45% of the latter. In no other particular did so great a discrepancy between the two groups emerge.

Dr. J. K. RUSSELL (Durham) hoped to shed some light on the aetiology of male subfertility by a comparison of 100 men whose wives had had two or more living children, with 120 subfertile men whose wives had failed to conceive and whose sperm counts did not exceed 50 millions per ml. Little difference in physical characters in the two groups was seen, and the two poorest physical specimens were in the fertile group. There was no evidence that malnutrition or chronic infection was of aetiological importance. Varicocele, a history of operations on or near the genitalia, of venereal disease, and of sexual difficulties were encountered rather more frequently in the subfertile group ; but in fully half of these there was no clear explanation for the lowered fertility, beyond the probability of hereditary factors.

Dr. G. I. M. SWYER and Dr. P. E. HUGHESDON (London) reported testicular biopsy findings in a hypogonadal male which cast doubt on the validity of the generally accepted assumption that the histology of the fragment of testis examined at biopsy accurately reflects the structure of the whole testis. In this case the first biopsy gave a uniform picture of germinal aplasia, but a subsequent and larger biopsy showed the mixed pattern of germinal aplasia, complete tubular sclerosis, and full spermatogenesis.

### Biochemical Contraception

Drs. A. S. PARKES, F.R.S., H. ROGERS, and P. SPENSLEY (Mill Hill) discussed biological and biochemical aspects of the prevention of fertilization by enzyme inhibitors. The gentisic acid polymer, rehibin, a potent hyaluronidase inhibitor, regularly prevented fertilization of rabbit eggs when added to semen before artificial insemination, but, in addition to being insoluble and difficult to handle, it was wholly ineffective when given systemically to the does. A new phenolsulphonic-acid/formaldehyde polymer, also a hyaluronidase inhibitor, but more readily soluble, was similarly effective when added directly to semen, but ineffective systemically. The addition of further hyaluronidase to the inseminate restored the fertilizing capacity, and experiments involving the washing of spermatozoa after addition of the inhibitor showed that it acted on the hyaluronidase attached to the spermatozoa themselves. Various considerations cast doubt on whether the anti-fertility effect was due to hyaluronidase inhibition *per se*, and Dr. Parkes made it clear that the results so far did not suggest any practical use for these substances.

Dr. SPENSLEY discussed the biochemistry of the hyaluronidase inhibitors, of which there were five main groups, all possessing common features entitling them to the general description of "macroanions." They inhibited many other enzymes than just hyaluronidase, and it seemed probable that the anti-fertility effect was due to the formation of a layer covering vital parts of the spermatozoa.

Dr. T. MANN (Cambridge) discussed the biochemistry of spermicidal agents, which, he considered, fell into three main groups : enzyme inhibitors, sulphydryl combiners, and surface-active substances. Among the latter, several of the detergents, such as cetyltrimethyl ammonium bromide, were extremely potent. They acted by causing detachment of the lipoprotein layer from the surface of the spermatozoa, leading to leakage of intercellular elements.

There were three papers from the anatomy department of Liverpool University reporting further studies relating to spermatogenesis in the rat. (Professor R. G. HARRISON and Miss JEAN MACDONALD on the effects of low temperature on spermatogenesis ; Dr. E. W. MACMILLAN on the isolated caudovasal loop ; and Dr. E. J. CLEGG on the effect of arterial interruption on the fructose content of the coagulating gland.) Dr. CECILIA LUTWAK-MANN (Cambridge) reported some biochemical properties of the rabbit blastocyst, and Mr. M. W. H. BISHOP (Cambridge) described some aspects of the dilution effect in bovine spermatozoa. Dr. J. LOWENSTEIN (London) read a paper on mechanotherapy for erectile impotence.

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## LOCAL MEDICAL SOCIETIES

### Liverpool Medical Institution

An afternoon conversazione illustrating studies in inheritance was held on July 8 with Sir HENRY COHEN in the chair. Introducing the subject, Dr. C. A. CLARKE demonstrated simple Mendelian laws from hybrid butterfly experiments and showed that the same principles applied to heredity in man.

The exhibits were as follows: "Biochemical Mutants in Micro-organisms and in Man," and "Sex-linkage in Drosophila" (Dr. J. H. Burnett, lecturer in botany) ; "Simple Mendelian Laws Exemplified in Butterflies" (Dr. C. A. Clarke) ; "Achondroplasia in Man and the Cow," "Sex-linked Characters in Poultry," and "Microphthalmus in Pigs" (Mr. R. B. Maneely, lecturer in veterinary histology) ; "Genetic Tests in Man" (Dr. R. B. McConnell) ; "The Chances of Morbid Inheritance" (Dr. W. Howel Evans and Dr. J. C. Woodrow) ; "Rhesus-factor Inheritance and Practical Applications" (Dr. Anne McCandless, Dr. D. Lehane, Dr. F. P. Hudson, and Dr. K. McCarthy) ; and "Examples of Inherited Disease in Man" (Dr. Charles McKendrick and Dr. D. C. Watson).

# Correspondence

*Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.*

## A Danger of Surf-bathing

SIR,—A few days ago I attempted to resuscitate a drowned girl. She had been surf-bathing in a rough sea and was knocked down by a wave. Her struggles were seen by a friend, who immediately went to her assistance, and she was with great difficulty brought to land. The would-be rescuer paid for his gallantry with his life and was swept out to sea.

When I got to the scene, the patient had been placed prone on a tipped stretcher and artificial respiration had been applied for some time. It was immediately obvious that no ventilation was occurring, and on attempting to restore an airway it was clear that the mouth, pharynx, and presumably the tracheobronchial tree, were full of sand, seaweed, and regurgitated stomach contents which could not be cleared by posture or digital manipulation. At this point an ambulance was driven on to the beach, but, although the crew were eager and intelligent, they had no first-aid kit beyond an oxygen cylinder and B.L.B. mask. The feeling of frustration and distress at being unable to do anything effective must be experienced to be believed.

It would appear that this type of accident is becoming increasingly common, as seven such fatalities in one district were reported in three days in the daily press. It also seems probable that surf-bathing introduces fresh hazards in that the force of a wave (particularly if it is taken sideways) may stun an inexperienced surf-bather temporarily, and he then inhales a large quantity of sea-water containing sand. Unless he receives immediate help, the next breaker may completely overwhelm him. It would therefore seem that surf-bathing accidents occur much more quickly than in the case of swimmers being gradually overcome by adverse currents or rough seas, and there is more likelihood of the respiratory passages being filled with semi-solid contents instead of pure sea-water.

I would therefore like to make the suggestion that appropriate first-aid kits be kept in every ambulance operating near surf-bathing beaches or at a first-aid point on shore. The objection that anything portable is stolen could be overcome by enclosing the instruments in a strong locked box, the key of which should be in the custody of the ambulance driver or first-aid post attendant. This box should not be opened except on the request of a doctor, who is usually on the scene within a few minutes. The suggested kit should include: one full oxygen cylinder with reducing valve; one rebreathing bag and two face-pieces for lung inflation; one suction pump to work from oxygen cylinder with two assorted coudé catheters for tracheal and bronchial suction (a large 3-holed Teeman urethral catheter can be used); one direct-vision laryngoscope with two different-sized blades; two artificial airways; one bronchoscopy forceps.

It does not require the skill of an anaesthetist or E.N.T. surgeon to expose the glottis of a drowned person, and if one life a year was saved by these means it would surely be well worth while.—I am, etc.,

London, E.C.1. C. LANGTON HEWER.

## Warmth in the Treatment of Shock

SIR,—I agree with Dr. W. N. Leak's thesis (*Journal*, July 24, p. 240) that shock is a purposive mechanism, but I would disagree with some of his terms. He calls the use of warmth "traditional." Surely a traditional method is one that has been practised for a long time and is still practised. When it has been discredited and abandoned it becomes "historic"; when discredited but still practised it is "wrong." Again he calls the use of warmth "the treatment of symptoms." I was taught that a symptom is something complained of by the patient, whereas a sign is something discovered by the doctor. The shocked patient does not complain of cold; he desires it, he knows it helps him, and he spends his dying strength in attempting to throw off the blankets and shock-producing electric cradles heaped upon him by well-meaning but ignorant attendants.

If Dr. Leak is right, and the treatment of shock by warmth is still "traditional," the last war has, surgically speaking, been fought in vain. The efficiency of the circulation depends on the force of the pump, the volume of circulated fluid, and the peripheral resistance. In the shock of wounds or burns the volume is deficient, in the shock of coronary infarction the pump is damaged, but in both the peripheral resistance is doing its best—by cutting off the blood from the surface vessels to make an adequate amount available for the organs essential to life, the brain, the heart, the kidneys, and the liver; by cooling the body, to reduce the needs of the tissues for oxygen. Shock is a physiological phenomenon, and only with the appearance of secondary factors due to deficient oxygenation or bacterial decomposition does it become pathological. The treatment of shock by warmth can no longer be excused as "traditional" or "symptomatic." It must be condemned as "ignorant" and "dangerous."—I am, etc.,

London, W.1. HENEAGE OGILVIE.

SIR,—I have read with great interest Dr. W. N. Leak's letter (*Journal*, July 24, p. 240) on the above controversial subject. It seems to me he puts the case against warmth admirably, and as I have long entirely agreed with his views I should like to support him.

As a surgical specialist in casualty clearing stations in the 1914 war I noticed that men with severe wounds after journeys of hours from the line often arrived cold but in fair condition, and often after the customary process of warming up passed into a condition of irreversible shock and were never fit for operation. In the second world war, working at the casualty hospital at Dover, I found myself at first in a minority of one in opposing the use of electric cradles for warmth, but experience seemed to confirm my views, and I was delighted when, towards the end of the war, the R.A.M.C. brought out an admirable little pamphlet on shock which supported these. I trust that if I am unfortunate enough to have a coronary thrombosis someone will give me morphine and no one will warm me up.—I am, etc.,

Dover. A. R. JORDAN.

## Chlorpromazine and Agranulocytosis

SIR,—Chlorpromazine is becoming increasingly widely used both in psychiatric and anaesthetic practice. Several authors have reported a leucopenia occurring at various stages in the course of treatment, but more particularly in the earlier stages. As far as I know, however, no case of agranulocytosis has yet been recorded. The following case is therefore probably of some interest.

The patient, a woman of 69, was first admitted to hospital on July 25, 1952. She was suffering from a chronic depressive state as a result of which she became from time to time agitated and emotionally unstable. She was started on chlorpromazine 50 mg. three times a day on May 26, 1954, and remained on this dosage until July 5, by which time she had had a total dosage of 6 g. She was then noted to be very flushed and her temperature was 100° F. (37.8° C.). No abnormalities were found on physical examination either then or subsequently. Urinalysis revealed no abnormality. Her blood count showed: Hb 86%; R.B.C. 4,240,000 per c.mm.; total W.B.C. 680 per c.mm., with only 11% polymorphs. The drug was stopped immediately and penicillin was started. Between July 5 and 15 the blood count varied between 480 and 790. She was given five injections, each of 50 mg. cortisone, and from then onwards the W.B.C. rose rapidly, being 5,300 with 75% polymorphs by July 21.

The only other drug this patient had had since admission to hospital in 1952 had been chloral, and, as the white count returned so promptly to normal after withdrawal of the chlorpromazine, it seems reasonably certain that agranulocytosis can be attributed to this drug.—I am, etc.,

London, S.W.17. J. LOMAS.

### Dashboard Fracture of Patella

SIR,—As one who at the age of 59 sustained a dashboard fracture of my right patella involving the inferior portion of the bone, I was much interested in the article on this subject by Mr. I. S. Smillie (*Journal*, July 24, p. 203). I consider it an admirable summary of the mechanism, physical signs, and treatment of this injury. Like the case he quotes, I was unaware of any serious injury until I emerged from my car to inspect the damage and my right leg collapsed. I was treated by Mr. Charleson, of Perth (to whom I am everlastingly grateful), by excision of the lower fragment, the ligamentum being stitched on to the upper fragment and the lateral tears in the capsule being sutured. The result is very satisfactory. I have a loss of only about 5–10 degrees of flexion, and a stable painless knee. I have since climbed Lochnagar and many other lesser hills without any reaction in my knee, and can dance an eightsome or a foursome reel almost as well as ever I could before the accident. I realize I am lucky, and how well I was treated.—I am, etc.,

Aberdeen. R. R. M. PORTER.

### Harmful Certification

SIR,—For those willing to learn, Aesop's fable of the shepherd boy who cried "Wolf, wolf," teaches us that "a liar will not be believed, even when he tells the truth." For the most part patients are not such fools as Professor Lambert Rogers (*Journal*, July 24, p. 241) would lead us to believe. They come to learn whether a doctor tells the truth or gives soft words in an attempt to ease. In my experience patients with cancer seldom ask if their complaint is cancer; only one who had it ever asked me; they give the impression of knowing at the bottom of their heart. On the other hand, many whose complaint is not cancer ask if it is, and the amount of reassurance they get on being told "no" will depend on their estimate of the doctor's truthfulness. If a patient is not told the truth, nor given an honest prognosis, how can he hope to make a satisfactory mental and spiritual adjustment to his life? Does Professor Lambert Rogers think it right that a woman who has had an abdominal operation should leave hospital without knowing what has been done? Years after she may go abroad, have a recurrence of trouble, and be unable to tell her new doctor what was done.

A patient who asks should always be told the truth. A first certificate rarely carries such a definite diagnosis as disseminated sclerosis; and, if the patient has not asked, the first used cause can be continued.—I am, etc.,

Pettswood, Kent. G. C. MILNER.

### Drinking Sea-water

SIR,—May I reply to Dr. T. T. Chapman's letter (*Journal*, July 24, p. 246), and try to make it quite clear why even limited amounts of sea-water are harmful to castaways?

Sea-water is strongly hypertonic to human body fluids, and the first effect of absorption of any quantity of it, large or small, must be to increase the salt concentration of the body and so worsen dehydration. This rise in concentration could only be prevented if, first, the salt was excreted, and, secondly, this was accomplished with the expenditure of less water than the volume of sea-water which had been drunk. It has consistently been found that when a sea-water ration is given to dehydrated men the salt is not at first excreted. Both the water and the salt are retained in the body in roughly their original proportion, and balance studies of water and electrolytes have confirmed that the osmotic concentration of the body rises.[1 2 3] Later, the output of salt in the urine increases, but this is accompanied by a greater output of water, and the body is always left more hypertonic than it would have been if the sea-water had not been drunk. Diluting sea-water with fresh-water rations makes no difference to the result: men who do this will become more dehydrated than if they drank the same ration of fresh water alone.

Ladell's calculation,[1] to which Dr. Chapman refers, was based on the belief that, if the concentration of salt in urine was initially below the known maximum of about 2% sodium chloride, salt could be added to raise the concentration to this level without an increase in the volume. Later work has shown that this is not so: the urine formed during dehydration is already being concentrated up to a maximum osmotic pressure, and any addition to the solutes being excreted inevitably increases the volume. Increasing the solute output also progressively lowers the maximum osmotic pressure which can be reached.[4 5 6] It is interesting to note that, if the whole osmotic concentration which can be achieved in urine could be devoted to salt, a urine with a higher salt concentration than sea-water might be excreted (the osmotic concentration of sea-water is about 1,200 m.osmol./l. and that of maximally concentrated urine up to 1,400 m.osmol./l.). Urea, however, is being continuously excreted, and the quantity which reaches the urine accounts for a half or more of the total concentration. This leaves a maximum of only about 700 m.osmol./l. for electrolytes, corresponding to 2% of sodium chloride. This applies to an increment to an initial volume of urine as well as to the total volume, for, as Ladell observed, an increase in volume is accompanied by an increase in the output of urea.

Dr. Chapman's experiments are of great interest. I should, however, like to make the point that McCance and I used a carefully controlled and crossed-over experiment with several subjects to investigate the effects of adding 150 ml. sea-water to the daily water ration. I think it would need a very elaborate experiment to distinguish the effects of so small a quantity as 60 ml. from individual and chance variations. I would endorse Dr. Chapman's advice that there is nothing to be gained by spinning out a small water ration unduly. Finally, I can confirm that, from the point of view of water economy, about 100 g. is probably the optimum amount of carbohydrate to include in rations. By virtue of its protein-sparing action this amount will save more than its own weight of water, and its inclusion is therefore worth while, however limited the total space available for carrying rations. It will also prevent the starvation ketosis which Dr. Chapman refers to earlier.[3 7]—I am, etc.,

Cambridge. G. R. HERVEY.

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SIR,—As Dr. G. R. Hervey has quoted me in his letter (*Journal*, June 26, p. 1494) exposing the underlying fallacy of drinking sea-water, I would like to take this opportunity of renewing my friendly argument with him on this subject, and also of defining my own position. I am not, and never have been, an advocate of indiscriminate and unlimited drinking of sea-water; Dr. Hervey unfortunately does not make this quite clear in his letter. Moreover, the experiments he carried out with Professor McCance[1] were somewhat different in aim and conception from those I did for the M.R.C. Committee on the Care of Shipwrecked Personnel. My assignment was not, primarily, to find means of prolonging a castaway's overall survival time, but, for reasons which were made plain to me, to maintain him at as high a level of physical condition as possible for the first week or ten days in the boat. My first suggestion, which was adopted by the Committee,[2] was that the limited water ration should be consumed during this period and not spread out to last, as often happened, for a hypothetical 40- or 50-day voyage.

While carrying out these tests[3,4] it occurred to me that the total osmotic space available in the urine might not be filled; earlier work by Gamble and others[5] on rats suggested this possibility. I also argued that if a diuresis resulted from drinking a small quantity of sea-water the total osmotic space of the increased urine volume might be enough to accommodate both the obligatory urea and metabolite excretion of a semi-starving individual and also the salt of the sea-water; if the diuresis was less than the volume of sea-water drunk, then the man would benefit by the difference. The results of experiments did not entirely come up to expectations. In all cases the greater part of the extra salt was excreted, but in no case was it all lost, and the water gain, though real, was small. As a result, there was an increased hypertonicity, compensated for in part by a transfer of water from the intracellular to the extracellular compartments. But this movement, although hastening the final onset of fatal intracellular dehydration, does serve to maintain a shrinking extracellular fluid, and hence plasma, volume. It is only an exaggeration of the normal physiological response to water deprivation, and, while it continues, the "signs of dehydration," to quote Dr. Hervey, are in abeyance; disabling circulatory failure is, in fact, being staved off. Intracellular dehydration does not appear to show much effect until it becomes gross; then the moment of reckoning comes. In acute experiments in "hot-rooms," for example, a sweating man drinking hypertonic saline maintains perfect circulatory condition and feels fine, then suddenly he collapses completely. In both acute and long-term experiments I have found that a man drinking saline or sea-water remains in better condition, as judged by pulse rate and blood pressure, than the man who takes none. It paid to be in good condition for the first week adrift.

We never took more than 400 ml./day of sea-water in any experiment. In the longest experiment, lasting 10 days, the dose was 180 ml./day. In this experiment the total fresh-water intake for 10 days was 2,940 ml., and the subjects were on a dry diet containing not more than 5 ml. water. One group of men had no sea-water supplement, and the other a supplement containing 6.3 g. of salt. The difference between the urinary salt losses of the two groups indicated the amount of added salt excreted, and this fell short of the amount ingested by 17.9 g., but of this deficit 8.5 g. was due to retention on the first two days of the salt regime; this suggests that most of the "damage" is done on first going on to salt. But how severe is this damage? The men drinking sea-water had 4 mEq/l. more chloride in their plasma than had the others, and more sodium, and an increased hypertonicity; the plasma potassium was also slightly higher, by 0.5 mEq/l., due, presumably, to the passage of intracellular fluid outwards. Clinically, however, there was no difference between the two groups, both of which were still on their feet at the end of the 10 days. The men who drank sea-water were certainly no worse off, and I still think they were slightly better; their weight loss was 10%, compared with the 11% for the other group. Another week might have seen the sea-water drinkers collapse and the others not, but we were not interested in what happened then.

In the light of subsequent experience, however, I agree I may have erred in over-emphasizing the possibility of benefit from drinking sea-water in small quantities. Were I writing up this work now my attitude would be that, although no immediate deleterious effects may follow from drinking small, strictly limited, quantities of sea-water, it is highly dangerous to exceed these limits. I certainly would not endorse the Committee's wartime recommendation that rinsing the mouth out with sea-water is permissible, as each rinse means that at least 10 ml. of water is left in the mouth, and with frequent rinses the upper safe limit of intake would soon be reached. I was unhappy about this at the time, but I had preached better than I knew. I am still more unhappy about it now.

The real touchstone of sincerity in this matter is for the worker himself to say what he would do if he found himself adrift with the Board of Trade water ration of 112 oz. (240 ml./day for 14 days). If my chances of being picked up at all depended on my keeping fit and alert for the first week I would certainly drink some sea-water, but not more than 250 ml./day. If my chances of rescue depended on my remaining alive for the maximum length of time I would avoid sea-water. I would refrain from drinking anything at all for the first 24 hours, or until my urine had become concentrated and my excretory rate was down to 0.5 ml./min., as any water taken before this point is reached is lost in a diuresis. If allowed, I would drink most of my allotted water in the first 10 days. I would refuse protein or salty foods such as pemmican. My own ideal shipwreck ration would be 75% carbohydrate and 25% fat, the latter for palatability and interest, important even on a 500-calorie daily diet. As air temperatures at sea-level are the same as the water temperature, which rarely exceeds 29° C. even in the Indian Ocean,[6] provided there was some shelter from the sun (most important in a lifeboat), and I was not rowing, I would be unlikely to sweat no matter where I was. But if I did sweat, I would, paradoxically it must seem to Dr. McIlrath (*Journal*, May 29, p. 1264), immediately stop taking sea-water. Sweat is only about one-third as concentrated as body water; hence when body water is lost as sweat two-thirds of the salt that was dissolved in it remains in the body, further increasing the concentration. Losing a litre of sweat is roughly the equivalent of taking 5 or 6 g. of salt, which would indeed hasten the onset of lethal intracellular dehydration.

But after all this theory is there no medical "survivor," other than experimentalists, who can give us a first-hand account, not of what they set out to do, but of what they had to do?—I am, etc.,

Lagos, Nigeria. W. S. S. LADELL.

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2 Medical Research Council (1943). *A Guide to the Preservation of Life at Sea after Shipwreck*. War Memorandum No. 8. London.
3 *Lancet*, 1943, **2**, 441.
4 *Brit. med. Bull.*, 1947, **5**, 9.
5 *J. biol. Chem.*, 1932, **97**, 57.
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## Isoniazid and Weight Gain

SIR,—Referring to the article "Isoniazid and Weight Gain," by Dr. I. S. Mudie, Dr. N. W. Horne, and Professor J. W. Crofton (*Journal*, June 5, p. 1304), I should like to report on a similar investigation we started on infants in 1951.

We studied two groups: one in our children's wards, composed of six infants admitted for malnutrition, and a second one consisting of six healthy infants in a baby home. In none was there a family history of tuberculosis, and all had a negative Mantoux test. The dosage of isoniazid was 5 mg. per kg. of body weight, per day. The first group was observed for four weeks, receiving treatment for the first three weeks. The increase in weight was not remarkable. In all there was a fall in the haemoglobin values, ranging from 1–4 g. per 100 ml. The second group was studied for four months, receiving treatment four weeks after two months' observation. They were checked for another month after the isoniazid trial. In only two of them was there an increase in weight averaging more than the increase two months prior to treatment. In three of them there was a fall in haemoglobin of 1 g. per 100 ml. on the average.

Because of the disappointing results we stopped the trial and did not publish the results.—I am., etc.,

Haifa, Israel. ZWI LARON.

## Dental Extractions for Children

SIR,—I agree with Dr. Victor Goldman (*Journal*, July 17, p. 173) on the infrequency of the need for domiciliary anaesthesia in connexion with dental extractions. The average child meets the experience of dental anaesthesia with a commendable courage and interest. It requires the exercise of common sense on the part of both parent and anaesthetist to stimulate the courage and interest of the reasonably timid; and it may require the exhibition of

firmness and calculated lack of sympathy to bring the opinionated to their senses. With these categories there is no real problem, and in my opinion the use of barbiturates as premedication may upset the young patient's balance and self-possession.

But I cannot accept Dr. Goldman's method of dealing with the "unreasonable" child, seldom seen though such a child may be. The suggestion that the speed of a "vinesthene" induction robs the experience of any risk of psychological upset is, at best, specious. The journey from full consciousness to anaesthesia in such cases loses none of its terrors and despairs, reasonable or unreasonable, by virtue of its shorter duration. My own practice aims at never forcing an anaesthetic on an unwilling child: those who are really "unreasonable" and continue resistant to explanation and persuasion are premedicated with "seconal" (quinalbarbitone) to the point of basal narcosis, either there and then for induction of anaesthesia in an hour, or the requisite capsules are given to the parent for administration to the child before his next visit to surgery or hospital, depending on the urgency of the dental condition.—I am, etc.,

Rochester. GEORGE H. STUART.

## A Mouthful of Wire

SIR,—What is the opinion of the medical profession on the new craze for filling children's mouths with plates and plastic or metal contraptions in order to straighten teeth or alter the shape of the jaw?

As the headmistress of a school where more than a dozen of the children are afflicted in this way, I should be glad to know if it is really necessary. The children cannot speak properly and can take no pleasure in verse-speaking, or drama or singing lessons, or reading aloud; they find eating difficult and develop unpleasing habits, constantly putting their fingers into their mouths to fiddle with the things. In some cases their nerves are affected by the discomfort and they become tearful or irritable. The plates need frequent adjustment and the wires are constantly breaking. Every time this happens the children miss a half or whole day's school going to see the dentist; and, as the discomfort is acute when the wires break or become displaced, emergency appointments have to be made, at great inconvenience to all concerned. In a boarding school it is a major and recurrent nuisance.—I am, etc.,

Wirral. MABEL E. CARTER.

## Blood Changes Associated with Disseminated Tuberculosis

SIR,—With reference to Dr. J. R. Fountain's article (*Journal*, July 10, p. 76) and the letter by Drs. Jane M. Fullerton and A. G. C. Cox (*Journal*, July 24, p. 243), I would mention that the association of aplastic anaemia with disseminated tuberculosis has been recognized for some years as a clinical entity and formed the subject of Dr. F. B. Smith's presidential address to the Association of Clinical Pathologists in 1949.

The condition often appears to be part of a tuberculous septicaemia rather than the characteristic miliary form, and massive invasion of many organs by tubercle bacilli can sometimes be demonstrated. In view of the risk of infection, it would seem that considerable care should be taken in performing necropsies on atypical cases of aplastic anaemia.—I am, etc.,

Godalming. W. K. TAYLOR.

## Fractures Complicating E.C.T.

SIR,—I am sure that the majority of psychiatrists using E.C.T. will agree with Mr. J. P. Kelly (*Journal*, July 10, p. 98) that the references quoted in your annotation on "Fractures Complicating E.C.T." (*Journal*, June 19, p. 1428) show an alarmingly high incidence of this complication, which, I believe, is certainly not experienced in the usual hospital practice.

Following a report by Ramin and Veit[1] on two cases sustaining fracture of the scapula, I recently investigated the whole of a series of cases for the year 1953, when one case of this series also sustained a fracture of the upper border of the scapula. During this particular year, 8,204 "straight" convulsions were given by electro-convulsive therapy (2,438 male and 5,766 female), and there were four fractures, an incidence of 0.05%. These were in-patient treatments, but at an adjacent busy out-patient clinic no fractures have so far been reported following the invariable use of muscle-relaxant drugs. In the report by Ramin and Veit mentioned above, they found an incidence of fracture of 0.09% using Glissando control in 5,300 treatments (2,200 male and 3,100 female).

For all of us whose duty it is to discuss with patients and their relatives the pros and cons of this still very valuable and, at present, indispensable means of treatment, it appears reasonable and just to point out that the benefit of this form of treatment in carefully selected patients far outweighs the relatively slight risk of this complication.—I am, etc.,

Macclesfield. F. H. CORBITT.

REFERENCE

[1] *Amer. J. Psychiat.*, 1953, **110**, 153.

## Familial Paget's Disease

SIR,—I was much interested in Dr. H. J. B. Galbraith's valuable contribution on familial Paget's disease (*Journal*, July 3, p. 29). It is perhaps worth mentioning that on occasion Paget's disease in the second generation may begin quite early in life. I have described elsewhere[1] a family in which the father suffered from generalized Paget's disease and two daughters presented before the age of 20 with bone changes in the maxilla which were eventually followed by osteoporosis circumscripta of the skull and Paget's changes in the pelvis.

Paget's disease may not cause any symptoms or deformity for many years, and, as Dr. Galbraith says, one case in four is diagnosed by chance at a radiographic examination undertaken for some other purpose. It would thus be of great interest, should it prove possible, to radiograph the younger members of the families Dr. Galbraith has described. In this way more cases of early Paget's disease might be brought to light, and, in particular, further examples might be found of familial osteoporosis circumscripta, which, so far as I know, has only been recorded on two occasions.—I am, etc.,

Newcastle-upon-Tyne. R. E. IRVINE.

REFERENCE

[1] *J. Bone Jt Surg.*, 1953, 35B, 106.

## General Practice in America

SIR,—I can endorse wholeheartedly everything Dr. C. M. Fleming has written in his article on general practice in America and Great Britain (*Journal*, June 19, p. 1391). As the health officer (M.O.H.) of a sizeable rural district in Massachusetts of 16 towns, with a population of upwards of 40,000, daily I come into contact with all phases of practice, and personally know and work with the 20 or so practitioners in the district. Most of those men and three women are in fact general practitioners. It is these individuals who staff the two local hospitals, some being on the staffs of hospitals in towns fringing the district. I know of no doctor who is not on some hospital staff. As the consultant in communicable diseases I serve on the staff of the nearer of the two hospitals to my health unit office. This hospital has 40 beds and 15 bassinets. It is graded "A" by the American College of Surgeons. To retain that rating the standard has to be high. There is the local staff made up of the practitioners in the towns served by the hospital, and an outside consultant staff, some of whom are eminent Bostonian consultants. The regular staff tackle over 90% of all the work both in their practices and in the hospital, the consultants being called in on those rarer occasions when some operation, or obstetrical case, or medical condition requires it. Cases that the family practitioner thinks are beyond his own skill or beyond the resources of the local hospital are referred mostly to Boston, as for example to the Children's Medical Centre. The

regular staff meet once a month formally on the third Thursday evening. At these meetings, in addition to hospital business matters affecting the administration and the medical staff, case histories, death reports, including pathological reports, lectures by guest lecturers, films, and so on are routine. There is a very real interest in these meetings and the hospital rating depends on regular attendance by all of the regular staff. The hospital has a laboratory carrying out complete blood chemistry, urinalysis, bacteriology, and so on, and is staffed by a pathologist (shared with an adjacent hospital), a bacteriologist, and a technician. There is an up-to-date *x*-ray plant served by a visiting radiologist. The hospital has a well-equipped out-patient department, and a fully equipped operating theatre and obstetrical service. It is indeed a most satisfying experience to work in such a facility and in company with such go-ahead progressive practitioners, the oldest one of whom is 75 years of age and by no means a back number.

However, one must add that all things, in so far as the practice of medicine out here is concerned, are not perfect either locally or elsewhere, and the other side of an otherwise stimulating picture is the fact that a completely satisfactory answer to the problems of a continuing rise in hospital and medical care costs, as well as in providing such to the public, has so far not been found. The question is under serious study. An office call averages $3, a home call $4, and a call at night or on a holiday may cost $6 to $8 on the average. The average practitioner on the east coast may earn upwards of $12,000 to $15,000, while on the west coast these figures may double or more (net). To get 24-hour medical coverage has been a serious problem, although the profession is alive to it and is doing a lot about it. The doctors are often badly distributed, tending to concentrate in hospital areas, with the rural areas suffering most. For example, in Massachusetts there may be one doctor to 5–600 population in the cities, with the ratio one doctor to 2,500 in the rural towns, many towns having no medical men resident at all. In some towns with a population as high as 3,000 there may be no resident doctor. These towns may suffer especially in getting emergency coverage. However, to make up for this it should be emphasized that (because of the hospital connexion) the rural practitioner practises often a higher standard of medicine than the general practitioner in the large city, many of the latter being unable to get a hospital connexion. Over-commercialism, perhaps the result of the lucrative nature of American medical practice, is a definite problem, as a recent lawyer–doctor fee-splitting case over automobile accident cases points out. Human nature being what it is, there are here, as everywhere, a few men in medical practice who are in it with the profit motive as the driving force. America also has a problem of the cults (in various guises) and a proportion of the population prefer such to orthodox medical practice. Some of these command quite a following, sufficient to give weight to their recognition by State legislatures. In closing, I hope that Dr. Fleming's stimulating article will do much to enliven British medicine, especially to give good general practice and the well-rounded, well-trained, and progressive family practitioner their rightful place.—I am, etc.,

Ayer, Mass. KENNETH I. E. MACLEOD.

## Coat of Arms

SIR,—In view of the several letters in the *Journal*, and the many that I have received, about the proposed coat of arms for the Association, I think that I ought to make it clear to all that this project has not been lightly or speedily undertaken, but has been treated with great care and due consideration.

The matter was first raised at Council early in the year, when it was discussed and passed to the Office Committee for detailed examination. The Office Committee held two meetings on the subject, and considered very many ideas and suggestions. After some time, a proposed coat of arms was put to the Clarenceux King of Arms for his expert advice and approval. The suggested arms were modified by the Herald in accordance with the laws of heraldry, but in keeping with the aims, objects, and ideals of the Association and its founder. The new coat was then brought before Council, who approved in general, and at the same time decided unanimously to present an achievement of arms to the Association as a gift—subject to the approval of the Representative Body. The Representative Body accepted the gift with approval, but asked Council to consider various points of detail. This is being done, and all serious, reasonable, and constructive criticisms have been brought to the attention of Council and of the Clarenceux King of Arms. No final decision will be made until the next Council meeting.

I should like to pay tribute to Mr. J. W. Tudor Thomas and to Dr. A. Macrae for the great help they have given to Council and to me, and especially for bringing to light the phrase used by our founder Sir Charles Hastings: "With head, and heart, and hand." I am glad to say that this has definitely been approved by the Representative Body (as reported in the *Supplement*, July 10, p. 37, in proceedings of the Annual Representative Meeting) as the motto of the Association, and is a splendid link between our past President, who used it as the theme of his presidential address, and our founder.

I do not intend to answer all the points raised by correspondents, as there is not the space or the time; I can only reaffirm that every one of these points has been before Council and been carefully considered by the King of Arms.—I am, etc.,

Reading. S. F. LOGAN DAHNE.

## Child Guidance Clinic

SIR,—It appears that it takes on the whole much longer to prove or disprove the value of a new method of treatment in psychological medicine than in other fields of medicine. This might be connected with the difficulty in evaluation specific to this particular field. The recent discussion on insulin treatment in this column is one example. After twenty years of experimenting the opinions on the value of the treatment still differ as widely as at the beginning. I believe the time has come to think of some scheme of centralized research, which might save a lot of money and —what is perhaps more important—a great deal of disappointment and suffering.

In my letter to-day I would like to draw attention to a field in psychological medicine where we continue to use a method only because we have used it for the last thirty years, in spite of the fact that the rationale of that treatment has completely changed. I am referring to the division of labour in the orthodox child guidance clinic between the psychologist who does the testing, the psychiatric social worker who handles the parents, and the psychiatrist who treats the child. Should this expensive and unrealistic division of labour be continued in face of the view which is more and more accepted by many of us that in the majority of cases the parents need the treatment and not the children?

As the psychiatric social worker is not trained on the whole to give deep treatment to adults, this system cannot fulfil its function. In some child guidance clinics the treatment of the parents could not even be transferred to the psychiatrist, as he, too, has not the proper experience to do it (although in an "orthodox" clinic this would not even be attempted, as it would be "against the rule"). Another difficulty is that it is not easy to make a triple division of a total situation, which includes the child, the parents, and their environment, etc. In some clinics the psychiatrist and the psychiatric social worker report to each other; many, however, admit that they do not have the time to do it very often.

For the last five years we have tried at the Social Psychotherapy Centre to solve this difficult problem by forming a group, which consists of the particular child and his parents, the psychiatrist (trained and experienced in child and adult therapy), the psychologist, the psychiatric social worker, the play therapist, and one or two pupils. We have

tried to integrate the child guidance department into the adult department. Experience has taught us that this method helps (1) to preserve the total situation, (2) to increase the understanding between parents and their children, (3) to cope with the treatment of the parents, and (4) to use in a more flexible way the abilities of each member of the team in each individual case.

I know this method is not new. Adler used it in similar form in 1914 and recently some clinics have rediscovered it. It appears to me, however, that a discussion in this column might help to speed up this development.—I am, etc.,

London, N.W.3. J. BIERER.

### Cortisone and Aspirin in Rheumatoid Arthritis

SIR,—The correspondence following the recent trial of aspirin and cortisone in rheumatoid arthritis (*Journal*, May 29, p. 1223) has again thrown up the commonly felt distrust of "statistical" trials.

Unfortunately, criticisms tend to be misdirected—for example, Mr. W. Grant Waugh (*Journal*, July 10, p. 99) first indicated how certain psychological factors might be (statistically) investigated, and then calls the factors imponderables. The cause for the distrust lies in the elaboration of certain "statistical" details which make the non-technical reader feel that everything must be "all right," although he cannot say why. The distrust itself is important enough; but the importance of its cause is crucial. For the details in question are *unutilized* ones, and thus are a symptom of incomplete analysis, or, more harshly, of the reporting of selected facts only. We are told, for example, how the patients were stratified by sex, age, treatment-centre, and duration of symptoms; but nothing is said about the effects of these classifications. These factors have somehow "been allowed for," but how much more true to the facts, and also how much less "statistical," had we been told either that they did not matter in this study, or, if they did, how. Again, the sheep-cell agglutination test was used to give "evidence of the accuracy of the diagnosis"; but did positive and negative reactors differ therapeutically? Averages are tabulated in great detail, but without a mention of the size and nature of the scatter; we therefore do not know how general the results are (the bigger the scatter, the better). Percentages are reported although they add nothing to the conclusions (more generally, as it happens, any percentages would be misleading). Many different tests and assessments are used, but we are not told how they interrelate. And so on.—I am, etc.,

London, S.E.5. A. S. C. EHRENBERG.

### Appendix in Hernial Sac

SIR,—From my own experience I would agree that it is not uncommon to find a hernial sac containing an appendix, either alone or more commonly in company with other parts of the alimentary tract. However, it is very much less common to find pus and a ruptured gangrenous appendix in a hernial sac such as I recently encountered.

Pre-operatively in this patient it was considered that the sac contained strangulated small bowel, but it was noticed that the skin of the scrotum and lower abdominal wall was more widely inflamed than in most cases of strangulated herniae. At operation it was apparent that there was no obstruction or strangulation of the loops, but the surface of these loops was, of course, acutely inflamed. After removing the appendix the wound was left open, and no attempt was made at that stage to reduce the loops of bowel into the abdomen. After waiting six weeks for the inflammation to subside the wound was reopened and the hernia repaired by Dr. R. J. Malcolm, F.R.C.S.

Because of the letter by Mr. Robert I. Cohen on a similar subject (*Journal*, May 8, p. 1098) I am prompted to say that at no stage did we expect this patient to die, nor do we expect this to happen as a rule to patients with strangulated herniae who require bowel resection.—I am, etc.,

Sydney, N.S.W. EDWARD WILSON.

### Section of Dermatology at Glasgow

SIR,—As a junior—that is, non-consultant—dermatologist, I would most heartily endorse Dr. F. F. Hellier's appeal to the senior consultants (*Journal*, July 24, p. 247). We lesser lights have grown to recognize with sadness that a dermatological meeting is usually a sign for the chief to leave the clinic and the registrar to stay working even later than usual. It must also be emphasized that the cost of attending these meetings is not chargeable to an expense account when one is employed full-time in the N.H.S., and many hospitals are loath to permit study leave with pay unless a paper is to be presented to a society, and even then expenses are rarely paid (I believe this is particularly true of the provincial hospitals).

In order to help us attend such meetings I would therefore enlist the aid, not only of the consultants, but of the hospital boards, to loosen the purse strings slightly in favour of such attendances. If this could not be done, perhaps the B.M.A. could again attempt to obtain a ruling that full-time N.H.S. employees may claim travel and subsistence expenses off the income tax, in which case the advantages to be obtained from attending such meetings would cost a registrar only as much as it now costs a consultant.—I am, etc.,

Leeds. JOHN H. S. PETTIT.

### Care of Old People

SIR,—I have been most interested in the various comments which have appeared in the Press on the subject of the International Congress of Gerontology which was held at Church House on July 19.

It may be of interest to your readers to learn that the International Hospital Federation held a Congress in Brussels as long ago as 1951 which had for its main theme the self-same subject as that which has been the object of such wide comment during the past week: the care of old people. Over 500 delegates from 25 countries attended this congress and took part in the discussions, which brought forth many useful and worthwhile ideas.—I am, etc.,

London, E.C.2. J. E. STONE,
Hon Secretary and Treasurer,
International Hospital Federation.

## POINTS FROM LETTERS

### Proposed Coat of Arms for B.M.A.

Dr. A. E. STEVENS (Jersey) writes: Your issue of June 26 deals with unrelieved gloomy subjects such as carcinoma of the stomach, oesophagus, rodent ulcer, and a modern counterblast against tobacco, which is our one remaining solace in this sorry world; but when I came to page 1491 my alarm and despondency were dispelled. Surely Clarenceux had his tongue in his cheek when he designed our coat of arms! Take the two supporters. Their birthdays are separated by no less than 2,088 years. Dexter, Hippocrates garbed in the fashion of Cos in 460 B.C. is warning us that "an apple a day keeps the doctor away." He is not realizing that he is in immediate deadly peril from the lion passant, and, worse still, from the fangs of the green mamba. Sinister, is Dr. Harvey wearing the professional kit of 1630. We now know he was left-handed and liked to play quoits.

### Alcohol

Dr. A. J. COLBY TINGEY (Epsom) writes: With reference to Dr. P. F. Chapman's letter (*Journal*, June 19, p. 1439), no man in his senses drinks alcohol; he takes wine, beer, or spirits, according to his taste or inclination. There used to be an aphorism: "What is the greatest blessing conferred by Nature on a long-suffering humanity?" The answer, of course, being: "The use of fermented and alcoholic drinks." For the corollary "What is the greatest curse?" the answer is: "The abuse of alcoholic drinks." . . . The intoxicating effect of fermented liquors is much less when they are taken as a beverage with meals. I would certainly agree that any person who consumes several drinks on an empty stomach and then undertakes to drive a car, or other mechanically propelled vehicle, is a menace to the public.

# Obituary

## T. W. LETCHWORTH, M.D., F.R.C.S.

We record with regret the death in London on July 22 of Mr. T. W. Letchworth, for many years consulting surgeon to the Royal Eye Hospital. He was 80 years of age.

Thomas Wilfrid Letchworth was born at Brighton on July 5, 1874, and was educated privately and at Emmanuel College, Cambridge. Receiving his clinical training at St. Bartholomew's Hospital, he qualified M.R.C.S., L.R.C.P. in 1898 and obtained the degrees of M.B., B.Chir. in the following year. He did not proceed to the M.D. until 1947, the degree being conferred on him a few weeks after his 73rd birthday. He was admitted F.R.C.S. in 1909. After graduation he was ophthalmic house-surgeon to Vernon and Jessop at "Bart's," where began his life interest in his specialty. He also held house appointments at the Wolverhampton General Hospital and at the Royal Hampshire County Hospital. He then gained experience in general practice for three years at Bournemouth, but from quite early in his career his real interest was in ophthalmology. Thus, in 1910 he became house-surgeon at the Royal Westminster Ophthalmic Hospital, where he came much under the influence of Brewerton, to whom he always acknowledged his great indebtedness. When he finally settled at Surbiton in 1911 it was as an ophthalmic surgeon. At the Royal Westminster he later became clinical assistant, holding a similar appointment at both the Central London Ophthalmic and the Royal Eye Hospitals, while in 1912 he became ophthalmic surgeon to the Marylebone General Dispensary. He obtained other honorary appointments at the Hampstead General Hospital (in 1913) and the Hospital of St. John and St. Elizabeth (in 1914).

It was at the Royal Eye Hospital, however, that he and his work were best known. Since 1919, when he was appointed surgeon to the hospital (later he became consulting surgeon), his skill as a specialist and his ability as a demonstrator, allied with his friendliness and good nature, have endeared him to all his colleagues, his students, and his patients.

A resident of Surbiton for over 40 years, he was well known and highly respected in the town and in the neighbouring Royal Borough of Kingston-upon-Thames. A member of the British Medical Association for over 50 years, he was chairman of the Kingston-upon-Thames Division in 1923–4, and he represented his constituency at two Annual Representative Meetings during the first world war. The last years of his life were saddened by the loss of his wife, formerly Miss Edith K. Worth, of Bournemouth, who died in December, 1951. He is survived by two sons and a daughter.

We are indebted to L. H. S. for the following appreciation: The late Thomas Wilfrid Letchworth was a man who inspired affection in everybody with whom he worked. He had entered the specialty of ophthalmology by the route of general practice, so that a patient was never simply an "interesting eye" but always an individuality. He took a personal interest in patients' families, and during his crowded out-patient sessions at the Royal Eye Hospital he would ask them in friendly fashion about other members of their families whom he remembered on previous visits. His appearance was striking, with a patriarchal white beard and eyes which twinkled benignly behind his glasses. This was combined with a complete lack of formality and an independent assessment of people on their merits, which sometimes proved disconcerting to the self-important.

Letchworth had a deep interest in mathematical matters, and this precision and formulation of thought he carried into his ordinary life. He was fond of refractive work, which he could execute with unrivalled accuracy at prodigious speed. He was a pioneer worker on muscle-balance, and invented a rotary prism of variable strength which he would demonstrate to admiring but not fully comprehending house-surgeons. He was interested in nystagmus, and it was characteristic that he trained himself to demonstrate voluntary nystagmus in amazing fashion. As an operator he was unsurpassed in his day. He had a light and exquisite sense of touch which enabled him to succeed in the most delicate manipulations. Yet his good temper was such that he never lost patience when training a beginner in ophthalmic surgery.

He was a great lover of chess, in which he achieved considerable distinction. Towards the end of his life he suffered a succession of tiresome and painful illnesses, which his devout Catholicism enabled him to bear with Christian fortitude. He will long be affectionately remembered.

T. M. T. writes: Letchworth retired from the Royal Eye Hospital on reaching the age limit in 1934, but with great humility and helpfulness he remained to act for three more years as honorary clinical assistant. He continued in consulting practice until three years ago, when he still kept on a small amount of work "to keep his hand in." During the first world war he was local secretary of the Kingston Division of the B.M.A., and after his busy day at the Royal Eye he would come home and work far into the night at this onerous duty, which included the office of secretary of the local medical war committee.

Letchworth was a most unusual and delightful character, of the type that is fast disappearing from the ranks of our profession. He had the most delicate sense of humour, and nothing delighted him so much as a sly leg-pull successfully carried out on some unwitting colleague. All those with whom he came in contact could not fail to be attracted by his kindliness, his unselfishness, and his wide knowledge. He was a first-class French, Latin, and German scholar, and could quote pages of Molière by heart. He was also a first-class mathematician and could put his knowledge in this sphere to practical use, as he was among the first to produce a variable prism for use in refraction work. To crown his academic career, at the age of 73, and after two cataract operations, he wrote an original thesis for his M.D. and took his degree on the same day that his son took his M.A. at Cambridge. He was particularly proud of this distinction and was seen only a fortnight before his death wearing his gown at a public function at the Royal Eye Hospital, to the delight of his old colleagues. It is by those colleagues and by a long succession of house-surgeons and students at the Royal Eye that Letchworth will be most missed: his fame as a teacher of ophthalmic surgery will be kept green by the number of operations popularized among them by his teaching, and still often performed by them. He was a first-class teacher, often using his ready sense of humour to illustrate his points. His bright eyes twinkling behind his gold-rimmed spectacles, and his straggly white beard, through which he constantly ran his fingers, will be recalled by many, as will the legendary stories of his amiable and harmless eccentricities.

Letchworth was very happily married. His wife died two years ago, leaving two sons and a daughter. Letchworth was a keen sportsman and was best known as a swimmer. He also was no mean chess player, and represented Surrey many times. Nothing in his life, however, gave him more pleasure than when his eldest son rowed twice in winning Cambridge crews in 1927 and 1928. Since his wife's death he had been somewhat less alert, though he died, as he always wished, in a light harness.

## MILNE McINTYRE, M.B., F.R.F.P.S.

Mr. Milne McIntyre, formerly professor in surgery at St. Mungo's College, Glasgow, died in a nursing-home at Glasgow on July 14, a few days before his 73rd birthday. Although he retired from active hospital work about fourteen years ago, he still continued in private practice until, a fortnight before his death, he underwent a serious operation.

Milne McIntyre was born at Govan on July 20, 1881, and was educated at Glasgow High School and at Glasgow University, where he graduated M.B., Ch.B. in 1905. He became a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow in 1916. Throughout his career as a surgeon his main association was with the Glasgow Royal Infirmary, where he went through the various junior grades, including that of assistant pathologist from 1910 to 1913, eventually becoming surgeon in charge of wards. He had a long and intimate association with Professor Peter Paterson, who occupied the St. Mungo chair of surgery from 1924 to 1935, and was for some years professor in surgery at St. Mungo's College, at that time the medical school of the Royal Infirmary. During the first world war he served as visiting surgeon to the Springburn Military Hospital from 1915 to 1918, and was casualty surgeon for the Northern Division at Glasgow from 1914 to 1921. Although McIntyre did not contribute a great deal to the medical literature, or take much part in the meetings of medical societies or in medical politics, he was a popular consultant among a wide circle of practitioners, who valued his advice and sterling character.

Milne, as he was affectionately known to all his colleagues, was essentially a shy man who disliked frills and ostentation in any form. He scorned the use of a motor-car, except in an emergency, and during his long hospital connexion used to walk the considerable distance from his house to the Royal Infirmary every morning, usually arriving before any of his staff. He loved his native country and was never happier than when spending a holiday in the Outer Hebrides. It was typical of him that when he had a sudden perforation of a duodenal ulcer some twenty-six years ago he himself telephoned one of his colleagues to give him the diagnosis: he had previously arranged for his own admission to a nursing-home and had fixed the time when he would be on the operating table. The arrangements were carried out to the letter. Glasgow graduates all over the world and a vast number of patients in the West of Scotland will mourn the passing of an excellent teacher and surgeon and a staunch friend. He is survived by his wife, formerly Miss Jean B. Anderson, to whom we extend our sympathy.—G. H. S.

## F. W. STUART, M.D., Ch.M.

Mr. F. W. Stuart, well known in Birmingham as an orthopaedic surgeon, died in hospital there on July 29, eight days after his 69th birthday.

A son of the manse, Francis Wilson Stuart was born at Gartly, Aberdeenshire, on July 21, 1885, and was educated at Gordon School, Huntly, and at Aberdeen University, where he graduated M.B., Ch.B. in 1909. He obtained his Ch.M. four years later, and proceeded to the M.D. in 1914. After graduation, he held resident appointments at hospitals at Aberdeen, Dundee, Bury St. Edmunds, and Coventry before finally settling at Birmingham towards the end of the first world war.

We are indebted to Dr. JAMES F. BRAILSFORD for the following appreciation: With the passing of Francis Wilson Stuart a prominent figure in the orthopaedic life of Birmingham has gone. Many cripples will sadly mourn his death, since for nearly 40 years he devoted his attention to the alleviation of their sufferings and disabilities. Those of his colleagues with whom he had been associated for many years knew him to be a loyal friend who was fearless in his support of any just cause; there are many who had reason to thank him for his kindly advice in the treatment of patients before and after operation. The orthopaedic nurses and electrotherapists had in him a champion who spared no effort to improve their training and secure its rightful recognition. He first went to Birmingham in 1912 as resident assistant surgeon at the Union Infirmary, and later, after serving in France in the first world war, he worked under the famous Birmingham surgeon, the late Mr. Jordan Lloyd. In 1917 he joined a team of orthopaedic surgeons as an assistant to the late Mr. Naughton Dunn at the Special Surgical Hospital, Hollymoor. Under the latter's influence he worked in the orthopaedic hospitals at Birmingham and Oswestry. His work at the Paybody (Coventry), Manfield (Northampton), and Warneford (Leamington Spa) hospitals brought him many grateful friends and colleagues. Recently the staff of the Royal Orthopaedic Hospital, Birmingham, made presentations to him and to Mrs. Stuart in testimony of their high appreciation of his devotion and friendship. As a constant close friend and colleague since 1917 I shall miss his kindly mannerisms and advice. He leaves a widow, two daughters, and a son, to whom we of the Royal Orthopaedic Hospital extend our sympathy.

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The death of Mr. C. E. S. JACKSON, at Thetford, on July 23 at the age of 66 will be mourned not only by his professional colleagues but by a large section of the general public in West Norfolk. The son of a doctor, Charles Eric Sweeting Jackson was born on March 19, 1888, and educated at Haileybury and at St. Mary's Hospital, where he qualified in 1911. In the following year he graduated M.B., B.S. He quickly made up his mind to specialize in surgery and took his F.R.C.S. in 1913. During the first world war he saw active service as a surgeon in France, gaining a wide experience in traumatic surgery which was of great help to him on his return to civilian life. Coming back from the war to his home town, King's Lynn, he carried on his father's general practice for a very short time, and then took the plunge and set up as a consultant—the first ever to do so in the district. His great ability and his painstaking care soon won him success, and he became firmly established in a consulting practice throughout West Norfolk and South Lincolnshire. J. L. writes: While Mr. C. E. S. Jackson made a great personal reputation as a surgeon, his greatest work was undoubtedly the modernization of the medical resources of the West Norfolk and King's Lynn Hospital, of which he was senior surgeon for twenty years. During this period he was a member of the governing board of the hospital, and it was largely through his initiative that it changed from a general-practitioner to a specialist hospital. His vision was not limited by his own department: by his influence other specialist appointments were made in the eye and medical departments. It is perhaps true to say that in those early days King's Lynn was unique among the smaller provincial hospitals of similar size in having its own consultant services. On the governing board he pressed for and obtained up-to-date equipment and a new outpatient and medical block. It was a great blow to himself and to his colleagues and friends in the district when, in 1938, he felt obliged through ill-health to give up surgical practice and retire. He was incapable of remaining idle, however, and during the last war took on a country practice in Lincolnshire, retiring eventually to Thetford, where he spent his last years still using his experience to good effect on the medical board at Cambridge. His last illness

was sudden in onset and mercifully painless and of short duration. Outside his practice he had many interests, and, while his health allowed, was a keen and very good if sometimes unorthodox golfer. I know of no other man who could consistently use a spoon in a bunker with such good effect. He was, in turn, chairman of the West Norfolk Division of the British Medical Association and president of the Norfolk Branch and a regular supporter of all Association activities. In addition, he served for a number of years as a borough magistrate and brought to the bench the same good qualities that gave him success in his work. He is survived by his widow and son, who is also a member of the medical profession, and to whom the sympathy of all in the district is extended. R. O. T. writes: I knew Mr. C. E. S. Jackson from his very early days as a consultant. As a "specialist" he was always kind and helpful to all his practitioners, and would turn out any time of the day or night in any weather if called on for advice and help. His surgical skill was limited only by what he believed to be his own capabilities, and he never hesitated to advise a further opinion if he thought fit. His rather blunt, forthright manner gave confidence to his patients and practitioners alike, and this brought him almost unlimited work. Before the days of private wards, and being inundated with private work, he founded a nursing-home in King's Lynn, which later was transferred to Gayton Hall, to meet the increasing demand for his services. As a man, he made many friends but few acquaintances, and his impressive personality is remembered to this day by many of us who were fortunate enough to call him in consultation. His health broke down and he retired to Devonshire in 1938, but his roots were in Norfolk and he returned to Leziate after a few months. During the recent war he was in harness again, running a practice at Gedney Hill, but his health was failing, and he finally retired to Thetford. So passes the man who helped to make King's Lynn Hospital what it is, a real friend and a loyal colleague.

Dr. A. H. ELLIOTT, who died suddenly at his home at Greenwich on June 20 at the age of 55, will be sadly missed by a great number of colleagues, friends, and patients. Abraham Hyman Elliott received his medical education at Queen's University, Belfast, graduating M.B., B.Ch. in 1920. He then held resident appointments at his own teaching hospital and elsewhere before settling at Greenwich in 1927. Although never very robust, he felt such great concern at the events leading up to the outbreak of the war in 1939 that he volunteered immediately and served in the R.A.M.C. in the Middle East from 1942 to 1946. While he was away his house was damaged in air raids, and with his unfailing good humour and gentle persistence he set about the task of rebuilding his home and practice. Unfortunately the hardships he endured during the previous years precipitated an illness in the summer of 1946, and from then he suffered continuous ill-health, though this did not deter him from working until the very end; he remained, as always, kind, considerate, and courteous to his patients. A most helpful colleague, he was also a most charitable man, both in public and in private, and was always one of the first to put his hand in his pocket. His offerings were usually accompanied with the request that his name should not be mentioned. He will be missed from the meetings of the West Kent Medico-Chirurgical Society, of which he had been a member for nearly thirty years. A loyal supporter of the Greenwich and Deptford Division of the British Medical Association, he was a member of its executive committee for many years, but to the sorrow of his colleagues he refused the chairmanship owing to ill-health. For a brief period in 1946 he was honorary secretary of the Division. He was a sound adviser, but never pushed himself to the forefront: his genial smile and apt phrase curbed the more turbulent spirits when tempers were short in 1947. He married in 1932, and he and his wife kept open house, to which everybody was welcome and in which friendliness prevailed for all their guests. The sincere sympathy of all his friends is extended to his widow, son, and daughter.—J. D. S. and J. M. L.

# Medico-Legal

## STERILIZATION AND DIVORCE

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The recent appeal[1] of Mrs. Iris Olga Bravery against the dismissal of her petition for divorce on the ground of cruelty, the cruelty relied on being that her husband had had himself sterilized against her wishes, caused an acute difference of opinion between the Master of the Rolls and Lord Justice Hodson on the one hand and Lord Justice Denning on the other.

In October, 1934, the parties were married. In 1936 a child was born. In 1938 the husband, who was a porter at the Royal Northern Hospital, underwent an operation for sterilization, the precise nature of which was not given in evidence. Thirteen years later the wife left home and never returned.

In the majority judgment of himself and the Master of the Rolls Lord Justice Hodson said that in their view the wife had wholly failed to prove the case which she sought to make, which was that her husband had had himself sterilized against her wishes, thereby causing a deep-seated and persistent grievance which resulted in a progressive deterioration of the marriage and in injury to her health or reasonable apprehension of injury, and making life so intolerable that she left her husband. No doubt for a husband to have himself sterilized without good medical reasons would be a grave matrimonial offence unless his wife consented, and would easily be held to be cruelty if it resulted in injury to her health. The operation, however, had taken a minor place in this wife's complaints, and they could not conclude that she had ever made any effective objection. She was living in the hospital and knew the surgeon and the nurse, and they did not believe that any surgeon, a member of an honourable profession, would sterilize a young married man unless first satisfied that his wife consented.

Lord Justice Hodson concluded by dissociating himself and the Master of the Rolls from Lord Justice Denning's view expressed in his dissenting judgment of the criminal implications of an operation for sterilization in the absence of "just cause or excuse." The question was not relevant to the issue in the appeal, and they were not prepared to hold in the absence of the surgeon or any representative of the hospital that the operation was done without proper justification.

Lord Justice Denning expressed the view that the only proper inference from the evidence was that the wife had not consented, and that the husband's conduct in having himself sterilized amounted to cruelty in itself. The effect was that the wife could not bear the husband near her, and this injured her health. He could think of nothing more disruptive of marriage than for a party to sterilize himself in this way.

In Lord Justice Denning's view, even if the wife did consent at the time she was not precluded from complaining when in later years the injury to her health was caused. When there was no just cause or excuse for such an operation it was unlawful even when a man consented to it. He quoted a case recorded by Chief Justice Coke in 1604 in which a "young strong and lustie rogue" got his companion to cut off his left hand so that he might avoid work and be able the better to beg. Both were found guilty of a criminal offence. An operation for abortion was unlawful unless necessary to prevent serious injury to health. Similarly, sterilization was lawful when done with consent for just cause—for example, to prevent the transmission of hereditary disease. When, however, it was done to enable a man to have the pleasure of sexual intercourse without shouldering the responsibilities attaching to it, it was unlawful even with the man's consent.

[1] *The Times*, July 27, 1954.

Lord Justice Denning said that the divorce court should not countenance an operation for sterilization without just cause or excuse any more than did the criminal courts, and he would have allowed the appeal.

It is not without significance that the Master of the Rolls's and Lord Justice Hodson's experience before they came to the Court of Appeal was in the Chancery Division and Probate Divorce and Admiralty Division respectively. In these jurisdictions judges and counsel are not normally concerned with the administration of the criminal law. In the Queen's Bench Division, where Lord Justice Denning's previous experience mostly lay, they are. There is little doubt that if ever a case of sterilization without good medical reasons—and "contraceptive sterilization" would be such a case—found its way into a criminal court, it would be held to be a criminal offence, consent or no consent. Happily it does not appear that such a case has yet come before the courts.

## LETHAL FUMES FROM JAM

Carbon monoxide poisoning caused by charring jam was the unusual cause of death in a case that came before the coroner at Sutton, Surrey, recently. A spinster, aged 65, was found by the police lying dead on the kitchen floor of her house. The room was full of fumes, and on one of the lighted gas rings stood a large bowl covered by a wooden lid. The bowl had contained jam, but it had boiled over and burnt dry. The lid was smouldering. The post-mortem examination by Dr. D. Haler, pathologist, showed that the woman had inhaled a considerable amount of carbon monoxide and that this was the immediate cause of her death. The appearances suggested also that she might have had a coronary attack, causing her to lose consciousness. Tests by the assistant chief physicist to the South-eastern Gas Board, Mr. J. B. Carne, showed that carbon monoxide was rapidly produced by carbonizing sugar, with the production of a lethal atmosphere. Returning a verdict of accidental death, the coroner, Dr. C. F. J. Baron, emphasized that there was no risk of carbon monoxide being produced in this way in the normal process of jam-making, but only when it went so far as charring.

# Medical Notes in Parliament

### Use of Trilene by Midwives

Miss FRANCES PITT (Birmingham, Edgbaston, Con.) asked the Minister of Health on July 30 whether midwives could now be authorized to administer "trilene" as an analgesic in childbirth. Mr. IAIN MACLEOD stated that the Medical Research Council had now, after prolonged investigations and trials, recommended that midwives acting on their own responsibility after adequate instruction be permitted to administer trilene with inhalers conforming to an approved specification. He was informed that the Central Midwives Board had accepted this recommendation, and he was in consultation with the board about the measures necessary to give effect to it.

### Irradiation of Food

Mr. PHILIPS PRICE (Gloucestershire, West, Lab.), on July 30, asked what research work was being carried out in this country on the sterilization of food by high-intensity gamma radiation, and what practical results had now been obtained.

Mr. J. R. BEVINS, Parliamentary Secretary, Ministry of Works, replying on behalf of the Lord President of the Council, said that so far as he was aware no research work was at present being carried out on the use of gamma radiation for sterilizing food, but during the last five years the Food Investigation Organization of the Department of Scientific and Industrial Research, in collaboration with industrial and other bodies, had been investigating the use of similar types of radiation—namely, $x$ rays and high-velocity electron beams. A report was being prepared for publication, and a close watch was being kept on all new developments. There were technical difficulties in the use of such radiations in industry. There was, moreover, uncertainty whether irradiated food could safely be eaten. There was in addition the question of the prevention of unpleasant flavours. No practical application of these methods of sterilization could yet be expected.

### Nutrition in Nigeria

Mrs. LENA JEGER (Holborn and St. Pancras, South, Lab.) asked the Secretary of State for the Colonies what facilities existed in Nigeria for study and research in nutritional problems on a permanent basis, as distinct from occasional visits from specialists. Mr. H. HOPKINSON, the Minister of State, replying on July 28, said that the Nigerian Government had a full-time nutrition adviser. Research on nutrition was also carried on at the University College of Ibadan and by the Hot Climate Physiological Research Unit. Further research work was being considered by the West African Council for Medical Research.

### Paired Limb Problem

Mr. J. SIMMONS (Brierley Hill, Lab.) asked the Minister of Pensions and National Insurance if he would investigate the effect on the paired limb of wearing an artificial limb from the purely physical, rather than medical, aspect, by means of an immediate and swift examination of 25% of 1914–18 limbless war pensioners. Mr. OSBERT PEAKE replied on July 26 that some 4,500 limbless pensioners of the 1914 war had recently been examined in connexion with the investigations of the Rock Carling Committee, and he thought they had better wait and see what that committee reported before making up their minds on this point.

Mr. SIMMONS said he was not concerned with the foibles of the medical profession and a medical examination, but an examination, say, by the welfare staff of the Ministry to see what the physical effect was of wearing an artificial limb—whether men were more quickly tired and more easily handicapped by advancing age as a result. Mr. PEAKE said he was uncertain what distinction between a medical and a physical effect Mr. Simmons was trying to draw, but he was sure the investigations of the Rock Carling Committee would throw light on the matter.

### Scottish Queries

Mr. HECTOR HUGHES (Aberdeen, North, Lab.) asked the Secretary of State for Scotland on July 27 if he would state the numbers of mental patients released from mental homes under his control in Scotland during each of the last five years; what provision was made for their after-care; and what records were kept of their lives after their release and with what results. Mr. J. STUART stated that the total number of patients discharged from mental hospitals in Scotland rose from 4,443 in 1949 to 5,888 in 1953. The care of patients discharged to guardianship in private houses remained the responsibility of hospital authorities. In other cases, where a discharged patient's own doctor needed help in providing any necessary aftercare, this could be obtained by attendance at an out-patient clinic, by seeking the co-operation of a psychiatric social worker, or by enlisting the aid of a voluntary organization.

Mr. D. PRYDE (Midlothian and Peebles, Lab.) asked the Secretary of State for Scotland if he would consider appointing specialist consultants under the Health Service in the growing districts of Dalkeith, Easthouses, Newtongrange, and Gorebridge. Mr. J. STUART stated on July 27 that the specialist services based on Edinburgh hospitals covered the whole of the areas mentioned, and the usual facilities for domiciliary consultation were available for those who were unfit to travel to hospitals in Edinburgh.

Mr. PRYDE asked when cortisone would be available in sufficient quantity to allow sufferers from rheumatism and arthritis to be freely treated in Scotland. Mr. J. STUART replied that supplies were increasing, but this was a potent drug which could have harmful effects, and experience of its use was limited. He could not forecast when it might become generally available without restriction.

# Universities and Colleges

## UNIVERSITY OF CAMBRIDGE

In Congregation on June 10 the honorary degree of Sc.D. was conferred on Sir Edward Charles Dodds, F.R.C.P., F.R.S., Courtauld Professor of Biochemistry at the Middlesex Hospital Medical School.

In Congregation on June 12 the following degrees were conferred:

M.D.—R. Crawford, J. S. Jenkins, H. K. Meller, R. A. Womersley.

M.B.—Mrs. Elizabeth A. Eldon.

Professor H. R. Dean has been elected to a Professorial Fellowship at Trinity Hall as from June 25, 1954, with seniority from the date of his original election on October 14, 1922.

The following candidates have been approved at the examinations indicated:

FINAL M.B.—*Part II:* [1 2 3]R. W. Ainsworth, [1 2 3]D. L. Almond, [3]J. Anderson, [1 2 3]P. C. Anderson, [1 2 3]P. C. W. Anderson, [1]W. Atherton, [1 2]D. W. Atkinson, [1 2]I. H. Backhouse, [1 2 3]J. Bamforth, [3]L. M. Barrett, [1]J. F. Bennett, [3]Mrs. A. B. Bentinck Speed, [3]L. J. Bishop, [3]G. D. Blackledge, [1 2]J. W. Blaxill, [1 2]L. H. Blonstein, [1 2]J. N. Bodger, [1]W. R. P. Bourne, [1 2 3]A. Bracewell, [1 2 3]J. P. Brady, [1 2 3]M. E. Budleigh, [2]D. C. L. Burges, [1 2 3]E. Burkinshaw, [1 2]J. R. Burwell, [1 2 3]J. A. Butler, [1 2]S. T. G. Butterworth, [2 3]P. G. T. Bye, [2 3]D. H. Cameron, [1 2 3]G. G. Carmichael, [1 2]R. A. Carpenter, [1 2 3]R. A. Carter, [1 2]S. B. Carter, [1 2 3]T. D. Carter, [1 2 3]J. D. Chard, [3]Mrs. A. Clarke, [2 3]T. R. Clendon, [1 2]J. R. Cobbett, [1 2]W. L. Cordeaux, [1 2 3]M. Cornelius, [1 2]I. J. Cour-Palais, [1]J. F. Crewdson, [1 2]P. D. Crockatt, [3]Mrs. E. J. P. Davies, [1]M. W. L. Davis, [1 2 3]E. E. Denman, [3]A. E. L. de Thierry, [1 2 3]B. H. S. Dixon, [1 2 3]W. D. Dolton, [1 2 3]H. Dovey, [1 2]J. A. Dryden, [2]J. P. English, [1 2]T. H. English, [1 2 3]J. M. Evans, [1 2 3]D. K. Fairweather, [1 2 3]D. T. Finlay, [1]I. McL. Flowers, [2]N. W. Fogg, [2 3]A. M. Freeman, [1 2 3]R. N. Galloway, [1 2]J. S. Garfield, [1 2 3]F. E. Garrad, [1 2]R. H. S. Gibbs, [1 2 3]R. K. Gilbert, [1 2]J. N. Godlee, [1]P. Gortvai, [1 2]J. V. Gosling, [1]C. M. B. Grigson, [1 2 3]J. N. Harcourt-Webster, [1 2 3]R. J. Haythornthwaite, [2]M. E. Hern, [1 2 3]K. W. Hickson, [1 2 3]C. P. Hindley, [2]M. Horowitz, [1 2]J. H. C. Hunt, [2]L. H. Hurrell, [2]J. Hurst, [1]R. D. Hyde, [1 2 3]R. B. Jenkins, [1 2]A. C. Johansson, [1 2 3]F. L. Johnstone, [1 2 3]D. H. Jones, [2]F. E. Kenyon, [2 3]P. J. D. Kirk, [2]H. W. Kirkpatrick, [1 2]A. H. Labrum, [1 2 3]W. G. R. M. Laurie, [1 2 3]E. P. Lawrence, [1 2 3]J. A. S. Lees, [1 2 3]M. J. Littlewood, [2 3]J. V. Longfield, [1 2 3]R. D. Lowe, [1 2 3]R. S. McKim, [2]R. F. McKnight, [1 2 3]I. E. McLaren, [2]J. R. McNeill, [1 2]S. M. Madeloff, [1 2]J. W. Maltby, [1 2 3]D. H. Mathias, [1 2 3]P. B. C. Matthews, [1 2 3]K. L. G. Mills, [1 2 3]C. J. Moore, [2 3]M. T. Moore, [1 2 3]R. M. A. Moore, [1 2 3]C. B. Mortimer, [1 2]M. T. C. Mower, [1 2 3]J. F. Mowbray, [1 2]R. C. Nainby-Luxmoore, [1 2 3]M. A. Newland, [1 2]W. S. Ogden, [2]K. R. Oliver, [1]P. J. J. O'Neill, [2 3]D. B. R. Osborne, [1 2 3]R. A. Owen, [1 2 3]R. W. Payne, [1 2]R. J. C. Pearson, [1]H. J. Pegg, [1 2 3]M. R. K. Plaxton, [1 2 3]A. Pollard, [1 2]J. B. Pond, [2]A. T. Porritt, [1 2]C. J. P. Potter, [1 2]D. J. H. Prosser, [1 2 3]D. Ratcliffe, [1 2 3]J. C. L. Rawes, [1 2 3]J. N. Rea, [1 2]E. Redfearn, [1 2 3]S. E. Reed, [1 2]C. F. Ridley, [2 3]J. R. Robertson, [1 2 3]A. Robinson, [1 2 3]B. H. B. Robinson, [1 2]M. S. Robson, [1 2]I. Ross Russell, [1 2 3]J. B. Royston, [1 2 3]A. O. Rusell, [1]C. E. Salter, [2]E. S. J. Samuel, [2 3]R. Schram, [1]A. D. Scott, [1]J. R. Scott, [1 2 3]G. G. Scott-Brown, [1 2 3]R. O. Selby, [1 2]A. J. Shaw, [1]M. P. Sherwood, [1 2 3]P. R. Shires, [1 2 3]R. G. D. Small, [1 2]G. W. T. Smith, [1 2]G. C. Spackman, [1 2 3]F. R. Spink, [1 2 3]J. A. Stamford, [2]G. P. Starck, [1 2 3]L. M. Stauffer, [1 2 3]R. M. Stirland, [1]S. G. Sutton, [2]G. F. W. Swan, [1 2 3]E. J. Tanner, [1 2 3]G. J. M. Thompson, [2]S. A. Tillyard, [1 2 3]J. E. Trapnell, [1]J. C. S. Turner, [1 2 3]A. S. Valentine, [1 2 3]I. H. M. Veitch, [1]R. J. Vince, [1]J. F. Walker, [1 2 3]C. A. M. Walkley, [1 2 3]R. S. Wardle, [1 2]N. A. Waring, [1 2 3]J. R. C. Weatherley, [2 3]D. N. Whitmore, [1 2 3]B. M. Wild, [1 2 3]J. C. Willan, [1 2]J. T. N. Williams, [1]W. D. W. Williams, [1 2 3]J. F. Wood, [1 2 3]B. Woods, [1]G. Yerbury. *Part I (Pathology and Pharmacology):* W. V. Agnew, I. H. Backhouse, D. J. Bartlett, W. R. P. Bourne, M. M. Brain, A. P. Brown, D. C. L. Burges, J. A. Butler, H. C. I. Bywater, F. G. Cooper, P. D. Crockatt, H. J. Davies, B. E. Farnham, I. McL. Flowers, R. N. Galloway, R. H. S. Gibbs, J. N. Godlee, J. V. Gosling, P. F. Gray, M. E. Happold, K. W. Hickson, J. Hurst, A. C. Johansson, H. W. Kirkpatrick, A. H. Labrum, D. H. Mathias, R. M. A. Moore, D. B. R. Osborne, R. A. Owen, H. W. Parry-Williams, H. J. Pegg, J. B. Pond, C. J. P. Potter, A. W. Prentice, D. Ratcliffe, C. F. Ridley, J. O. Robinson, M. S. Robson, J. B. Royston, C. E. Salter, R. Schram, A. D. Scott, P. H. Scott, A. J. Shaw, G. F. W. Swan, M. J. Turner, D. G. Twyman.

[1]Passed in principles and practice of physic. [2]Passed in principles and practice of surgery. [3]Passed in midwifery and gynaecology.

## UNIVERSITY OF GLASGOW

On May 1 the degree of M.D. was conferred upon H. G. Easton, J. T. Hutchinson, D. Macrae (*in absentia*; with high commendation), and J. Walker (with honours).

## UNIVERSITY OF ABERDEEN

At a Graduation Ceremony on July 8 the following degrees were conferred:

M.D.—[1]W. A. Cramond, [1]A. L. Speirs, [1]Elizabeth P. N. Turnbull (formerly Bell), P. H. R. Anderson, H. Brebner, S. Catterall, J. Fraser, W. Ironside (*in absentia*), T. Lyall, J. K. Russell, Lorna Wheelan.

PH.D.—F. E. Hytten, M.B., B.S.

M.B., CH.B.—[3]J. K. Finlayson, [3]Isabel M. Noble, [3]M. J. Williams, [3]W. Mc.A. Easson, [1]M. J. Emslie, [1]D. S. Robbie, [1]D-A. Aitken, [1]Myrtle Farquharson, [1]A. C. B. Dean, [1]Ena E. Thomas, Eleanor M. Adams, A. Addison, J. S. Allan, Valerie E. Anderson, Joyce D. Baird, J. W. Beveridge, A. J. M. Birnie, J. Bruce, D. Chalmers, A. J. Cheyne, Janet D. Davidson, I. Donald, J. C. Donald, W. Duncan, A. R. Duthie, Maureen B. Duthie, Doreen Ferguson, J. Forbes, F. L. P. Fouin, Fiona J. Fraser, I. C. Fraser, R. McW. Fraser, N. G. Fyvie, Helen A. Geddes, Joyce M. Gellatly, J. R. Gillespie, N. R. Gillies, Elizabeth F. Hamilton, J. H. Henderson, D. I. Hunter, H. A. Imray, J. D. Kinnell, Margaretta L. Laing, I. R. Lawson, H. J. A. Longmore, R. W. Macandrew, G. A. McDonald, K. J. MacDonald, Agnes M. McGlashan, Paula M. McKellar (formerly Angels), C. Mackenzie, F. A. Mackenzie, S. M. Mackenzie, I. A. Mackie, E. C. Macleod, J. L. Matthew, D. A. Middleton, Anne M. Mitchell, J. G. C. Munro, D. Murray, I. D. Neish, A. MacG. Nisbet, A. H. Park, A. G. Philp, Lora Y. Pratt, R. Ramkissoon, I. W. C. Reid, P. D. Robertson, C. C. Scott, D. C. Shillingford, A. G. Smith, H. G. Smylie, J. C. Steen, W. A. Stewart, W. E. Strachan, D. Stewart, J. S. Sutherland, Mary B. Symon, G. B. Taylor, J. F. Taylor, Mary Younie.

[1]With commendation. [2]With honours.

## UNIVERSITY OF EDINBURGH

At a Graduation Ceremonial held on July 21 the following degrees and diplomas were conferred:

M.D.—[1]R. D. T. Cape, [4]Mary E. Cripps, [1 4]J. A. Ewing, [2]R. H. Girdwood, N. D. Gunasekara, [1]R. M. Johnstone, A. Mories, [2]A. S. C. Peden, [1 4]I. H. Stokoe.

PH.D.—*In the Faculty of Medicine:* C. N. Crowson, M.D., E. E. Galal, M.B., B.Ch., E. Geiringer, M.D., A. H. Khan, M.B., B.S., J. A. Owen, M.B., Ch.B., C. W. M. Wilson, M.B., Ch.B.

M.B., Ch.B.—I. M. Adamson, J. W. Adamson, Isobel A. C. Alexander, G. C. Balleny, G. H. Begbie, J. G. Begg, W. H. Bisset, Biddy D. Bourhill, W. D. Boyd, J. R. Brunton, Joan M. Cairns, D. M. Cathro, Joan E. G. Caves, A. G. Collington, J. F. Comley, R. Condie, J. Cormie, I. D. S. Cowie, J. M. Davidson, J. N. G. Davidson, J. P. Davie, [5]I. W. Delamore, Gladys M. Dewar, A. Dick, T. E. Dickson, A. H. J. Dobson, A. J. Duff, Mary G. Dunlop, I. B. C. Eckford, K. D. Ellis, Freda W. Fleming, Susan M. Gaddum, I. D. R. Gordon, R. L. Grant, Dorothy L. Grieve, N. W. T. Grieve, Margaret S. Hall, I. H. Hallett, T. R. W. Hampton, W. J. Harvey, R. J. Hayhurst, I. D. Heath, Catherine Henderson, Rosemary Henderson, C. F. Hider, Margaret C. Holderness, Nancy M. Holmes, A. M. Horne, C. J. W. Huston, G. B. Hutchison, J. J. Jack, W. B. James, Elizabeth L. Jamieson, G. W. H. Jardine, T. G. Judge, S. C. Lauchlan, F. J. Lenman, I. G. Lennox, J. R. Liddell, W. R. McAinsh, A. P. McAllister, Avril G. McCowan, Fhiona M. A. McCracken, [5]F. B. McCue, G. M. McCulloch, Sheila McDonald, J. B. McDougall, J. A. McGechen, G. J. Mackenzie, Henrietta P. A. G. McNeil, R. A. Marshall, I. K. Mathie, Margaret C. G. Meikle, I. C. Menzies, T. W. P. Millar, W. N. Morley, I. G. Murdoch, That-Tze Ng-Lun, D. C. Oliver, Sheila G. Park, A. G. P. Paton, I. R. Pearson, D. M. Pendreigh, R. W. B. Penman, J. F. Pringle, J. L. Riley, Catherine W. Rintoul, H. K. Robertson, M. G. Robertson, A. Russell, J. C. Scott, J. R. Seel, W. T. K. Sellar, J. S. Shepherd, G. W. Simpson, H. W. Simpson, Torquil M. Sinclair, G. I. Slater, I. I. Smith, T. McI. Stevenson, J. A. Stewart, J. C. Stewart, D. Q. Sutherland, [3]J. Syme, C. M. Taylor, W. Urquhart, Asrat Waldeyes, Jean M. Walinck, R. G. Walker, W. J. Walker, H. G. Whiston, D. W. Williamson, Joan L. Young.

B.SC.—*In the Department of Pure Science:* Margaret F. Jamieson, M.B., Ch.B. (with first-class honours in bacteriology) [1]W. F. Coulson, M.B., Ch.B. (with first-class honours in pathology).

DIPLOMA IN PUBLIC HEALTH.—Freda M. Addly, W. L. Barton, Alison M. Battey, J. K. T. Cherry, Charlotte W. Cordin, K. S. Deas, Catriona M. Dempster, Isobel M. L. Forfar, I. A. Fraser, Monica C. Grant, A. T. G. Johnston, Natalie M. Johnston, P. D. Kemp, J. D. Kerr, Joan C. Main, K. W. Matheson, Helen M. C. S. Mowat, Eileen Reddy, J. L. Roche, B. Schulberg, E. B. Smith, J. F. Smith, D. Cameron.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—F. Bell, K. W. Blaikie, V. K. Dewan, J. Dubey, N. R. Eaton, D. MacL. Forsyth, A. F. Hutchison, T. S. Kalyanan, R. L. Kelly, M. V. Krishnamurthi, W. E. Laufer, Flora Murchison, H. V. Pophale, K. D. Saggar, V. Srinivasan, J. T. Worsfold.

The following prizes, scholarships, etc., were awarded: *Cameron Prize in Practical Therapeutics*, Sir Russell Claude Brock, in recognition of his work in establishing cardiac surgery on sound fundamental principles and in developing the operative treatment of lesions of the pulmonary valve. *Ettles Scholarship and Leslie Gold Medal in Medicine, the James Scott Scholarship in Obstetrics and Gynaecology, the Annandale Gold Medal in Clinical Surgery, the Keith Memorial Prize in Systematic Surgery,* and *the Murdoch Brown Medal in Clinical Medicine*, J. Syme. *Scottish Association for Medical Education of Women Prize* and *Mouat Scholarship in the Practice of Physic*, Margaret C. Holderness. *Dorothy Gilfillan Memorial Prize* and *Royal Victoria Hospital Tuberculosis Trust Gold Medal*, Dorothy L. Grieve. *Buchanan Scholarship in Obstetrics and Gynaecology*, Catherine Henderson. *Lawson Gifford Prize in Obstetrics and Gynaecology*, I. W. Delamore. *Beaney Prize in Anatomy and Surgery*. D. M. Cathro and F. B. McCue (equal). *Davidson Research Fellowship in Bacteriology*, Margaret F. Jamieson. *William Goodall Gibson Fellowship*, L. J. P. Duncan. *Wilkie Surgical Research Scholarship*, R. B. Duthie. *McCosh Bursary*, K. Krnjevitch. *Gunning Victoria Jubilee Prize in Child Life and Health*, T. T. S. Ingram. *Gunning Victoria Jubilee Prize in Therapeutics*, A. W. McI. Smith. *Singapore Gold Medal*, G. W. A. Dick. *Greig Medal for Tropical Medicine*, T. S. Kalyanam.

[1]*In absentia.* [2]Awarded gold medal for thesis. [3]Highly commended for thesis. [4]Commended for thesis. [5]Passed with honours.

## UNIVERSITY OF DURHAM

In Congregations on July 2 and 3 the following medical degrees and diplomas were conferred:

M.D.—A. H. Cameron, R. W. Scott, A. C. Jenkins (*in absentia*), E. S. Clarke, W. H. B. Ellis.

M.B., B.S.—W. K. Aitchison, Lilian F. Baker, Sheila Batey, E. S. W. Bidwell, P. R. Braithwaite, S. Brandon, A. G. Brown, W. B. Chamberlain, J. E. Charlewood, Edith M. Colling (*in absentia*), Margaret A. Conley, Helen M. Cowan, Margaret Crumpton, H. A. Davis, A. H. Dennison, Yves M. Dias, H. A. Dutton, R. W. Elliott, N. A. Elvin, R. C. F. Falckh, J. Foster, J. P. Gallet, Joyce Goldsbrough, J. Hall, W. Hazeldine, A. Hewitt, J. H. Hicks, C. D. Hierons, G. H. Hodgson, Susan M. Hodnett, J. H. Hudspith, J. McG. Jackson, N. Kirk, T. W. L. Knaggs, K. N Lockey, Jean M. McClory, T. McCree, W. L. Metcalf, G. D. Middleton, A. A. Milligan, T. J. Muckle, Jean Nicholson, D. A. Nisbet, M. F. J. O'Neill, W. Rand, B. B. Ratcliffe, K. J. Rees, B. Reffold, P. Richardson, Valerie J. Richardson, A. E. Ridley, J. B. Ross, Gwenda N. Rothery, M. Sabetian, J. Sarginson, A. Serck-Hanssen, Cicely M. Sewell, P. D. Smart, Ann Smith, G. Smith, A. P. M. Sowerby, Irene M. E. Thomas, A. Usher, G. Vasey, J. H. Walker, Mary C. P. Walton, A. J. G. Wilson.

DIPLOMA IN PUBLIC HEALTH.—G. H. N. Bates, Anna Book, A. Charlton, A. H. Fairlamb, P. F. A. Pereira, W. H. Suffield, H. C. Weir, A. E. Wright.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—J. C. Little, J. Murphy.

## UNIVERSITY OF LONDON

The following candidates at the London School of Hygiene and Tropical Medicine have been approved at the examinations indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN BACTERIOLOGY.—G. P. B. Boissard, P. Chadwick, E. D. T. Chapman, L. A. Hatch, N. A. Hinton, A. Q. Khan, F. N. Macnamara, B. P. Mishra, E. R. Mitchell, L. N. Mohapatra, Pauline M. Poole, J. A. Rycroft, Pui-Ching Wong.

ACADEMIC POSTGRADUATE DIPLOMA IN PUBLIC HEALTH.—G. A. Ademola, Doreen P. Allan, D. W. Boatman, S. C. Bose, H. H. S. Brown, J. Chatterjee, H. J. S. Coldham, C. P. Collins, L. P. Darmanin, N. S. Galbraith, G. S. Godiwalla, G. McL. Gorrie, Catriona M. Gourlay, A. Grut, K. L. Gupta, T. B. Harrison, [1]M. A. Heasman, F. M. James, H. James, B. Lall, R. J. Lande, I. Laufer, W. S. Millar, [1]S. L. Morrison, B. J. Ll. Moss, H.-H. Muller, [1]K. W. Newell, Joycelyn H. W. Newman, A. M. Nur, S. Ogen, T. A. Plumley, D. W. Quantrill, [1]C. J. Radway, D. H. Shennan, Rachel E. W. Sillett, C. Slome, C. I. Somaya, I. Suliman, R. J. K. Tallack, Pin Hui Teng, A. E. P. Twort, K. L. Vasa, R. B. Walker, F. A. Wickremasinghe, F. Zangen.

ACADEMIC POSTGRADUATE DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—A. E. L. Gunders, Y. J. Kiladjian.

[1]Awarded a mark of distinction.

## UNIVERSITY OF MANCHESTER

The following candidates have been approved at the examination indicated:

M.D.—*G. T. Ashley, K. Bloor, R. H. Broughton, P. Cole, *Kathleen V. Lodge, N. W. Preston, W. L. Tonge, A. N. Ashworth, *E. C. Hutchinson.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part II*: J. A. Krawiecki.

DIPLOMA IN PUBLIC HEALTH.—Pauline Blockley, P. V. Cant, J. Cragg, Irene E. Howorth, Susanne M. Lempert, Helen E. Mair, Barbara J. Nathan, T. A. Phillips, Fanny Stang, I. G. Taylor, Olive M. Thomas, Sheila M. Wheeler, A. Withnell.

FINAL M.B., CH.B.—G. M. Berlyne (with honours), Elizabeth K. Adam, Esther Almond, J. Alsop, D. N. Barber, A. M. Barlow, G. T. Bassil, M. S. Bourne, J. B. Buckley, Muriel Chadwick, J. R. Clyne, R. D. P. Craig, R. V. Dubberley, A. K. N. Dunton, B. Eddleston, W. J. Falconer, Jennifer M. Fowles, J. R. Freeman, I. Isherwood, D. M. Jones, Margaret P. Kenyon, D. C. Lamb, P. R. L. C. Lam-Po-Tang, Joyce E. Leeson, V. Lewis, B. Molyneaux, C. B. Moss, G. Newton, Margaret B. B. Norcott, Sheelagh M. O'Grady, Kathleen Parker, R. Postlethwaite, A. R. Robinson, A. H. Roscoe, Zena D. Rose, N. E. Seddon, N. A. Silverston, J. T. Spiller, D. A. Stott, O. Thomas, M. Tobias, Ruth M. Valentine, G. P. Walker, Alison G. Wallace, R. Waterhouse, D. Weinstein, E. I. Williams, G. C. H. Wilson, I. G. Yule.

*With commendation.

## UNIVERSITY OF WALES

At a Congregation held on July 22 the following degrees were conferred:

M.B., B.CH.—J. H. Jones (with honours), Sybil D. Bonvini, H. G. Bowen, E. F. Curran, G. R. T. Davies, J. Davies, C. E. Edwards, E. Griffiths, J. C. Griffiths, A. H. Haley, R. Harrell, F. Horsley, G. Howells, B. James, P. A. John, Audrey Jones, D. I. Jones, G. Jones, Gwendolyn A. Jones, J C. Jones, H. R. Kemble, B. H. Knight, R. K. Levick, A. F. Lewis, Pamela A. Lewis, E. H. Massey, H. A. H. Melville, P. C. Moore, K. Myers, H. K. Pachmayer, D. R. Pallas, Dilys Palmer, R. B. Payne, Auriel J. Reynolds, B. A. Richards, Joan M. Richards, D. F. M. Roberts, P. Rowlands, W. N. Schofield, Ann Thomas, D. J. Thomas, J. S. Wallace, Ursula Walters, Margaret M. Wilcox, Elizabeth D. Williams, Margaret N. Williams.

## UNIVERSITY OF BIRMINGHAM

In Congregation on July 3 the following degrees were conferred:

M.D.—B. N. Brooke (with honours), J. Hardwicke (with honours), J. D. Cruickshank, T. A. Lambo.

PH.D.—*In the Faculty of Medicine*: R. G. Record, M.D., D.P.H., D.Obst.R.C.O.G., K. W. W. H. Walton, M.D., and Sadek Hilali.

M.B., CH.B.—[1 2 3]K. J. Hadley (with second-class honours), A. S. Alvarez, I. B. Amara, J. Atkins, [4]T. R. Austin, F. Beck, M. G. Bhatia, F. Biddle, K. G. Bland, D. J. Boyles, Cynthia A. R. Bray, P. W. Brown, A. G. Chappell, H. Clamp, L. G. Cottrell, J. M. Davies, J. G. Domenet, R. A. Eames, J. M. Elliott, J. R. Elliott, C. Entwistle, Maureen Etchells, C. N. Faulkes, B. R. Freeman, Bridget M. Gell, S. D. Giddy, R. U. Gillan, A. Glass, I. M. Hadley, A. V. Hollingworth, Marion Hommers, M. J. Howell, [4 5]W. M. Huse, T. N. Iskander, Margaret A. Johnson, G. A. Jones, P. G. Jones, [1 6]L. J. Lawson, [7]I. M. Leck, E. A. Levene, B. V. Llywarch, P. J. N. McGuinness, W. T. McNeil, A. Martin, J. C. O. Mends, J. S. Milledge, Sandra Murdock, Margaret I. Naylor, F. G. A. Noon, M. H. Oakland, Margaret R. Palmer, [3]F. B. W. Parker, E. R. Perks, J. B. Reckless, J. A. Rigby, D. W. Robinson, T. W. Rogers, A. B. Rolfe, R. K. Rowley, H. A. Salmon, I. H. Seddon, J. I. Sellers, W. B. Shardlow, [1]J. M. Shephard, D. S. Smith, D. R. Smith, G R. Smith, B. K. Sood, [1]Barbara Y. Stockhausen, [8]Frances O. Thomas, M. A. Toseland, [8]Christine M. Walton, J. Waters, N. V. White, D. R. Whitehouse, [3]J. Williams, Joyce O. Yates.

The following scholarships and prizes have been awarded in the Faculty of Medicine:

*Queen's Scholarships.*—Final year, K. J. Hadley; Fifth year, Ann D. Braham and G. Horn. *Ingleby Scholarships*, Frances O. Thomas (obstetrics and gynaecology), J. Williams (paediatrics and child health). *Special Undergraduate Scholarships*, A. D. Barnes, L. S. Bernstein, D. C. Dukes, B. Goodhead, C. E. Oxnard, R. N. Smith. *Alan Brown Prize in Paediatrics* and *Priestley Smith Prize in Ophthalmology*, F. B. W. Parker. *Arthur Foxwell Memorial Prize in Clinical Medicine*, L. J. Lawson and J. S. Milledge. *Sampson Gamgee Memorial Prize in Surgery* and *Joseph Sankey Prize in Clinical Surgery*, K. J. Hadley. *Beckwith Whitehouse Prize in Obstetrics and Gynaecology*, Christine M. Walton. *"Queen's Hospital" Joseph Sampson Gamgee Prize in Surgery*, W. M. Huse. *Cyril Raison Prize in Surgical Diseases in Children*, J. G. Domenet. *Russell Memorial Prize in Nervous Diseases*, J. Williams. *Douglas Marsh Ear, Nose, and Throat Prize*, Joyce O. Yates. *Leith-Newman Prize in Pathology (Medical)*, Molly Hill. *Bertram Windle Prize in Anatomy*, W. A. Marshall. *Peter Thompson Prize in Anatomy*, Shirley M. Machin and D. M. Nicoll. *Foyle Prize in Pathology*, M. A. Woodhouse.

[1]With distinction in forensic medicine and toxicology. [2]With distinction in surgery. [3]With distinction in paediatrics and child health. [4]With distinction in pharmacology and therapeutics. [5]With distinction in pathology and bacteriology. [6]With distinction in medicine. [7]With distinction in social medicine. [8]With distinction in obstetrics and gynaecology.

## UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

M.D.—C. M. Ogilvie, J. P. Stanfield, T. D. Williams.

CH.M.—T. L. Schofield.

PH.D.—*In the Faculty of Medicine*: C. Harinasuta.

M.B., CH.B.—[1 2]Anne M. Godfrey, [1 2]Mary Gregson, [1 2]C. L. Imison, [1 2]N. C. Woodier, A. G. Bowers, M. J. A. Britten, N. T. Burnett, D. V. Coakley, R. W. Coffee, J. S. Comaish, J. R. Cope, W. P. Cuthbert, G. W. Danger, K. S. Davies, R. J. G. Downie, W. A. Downie, Florence M. Duckenfield, D. P. Duffield, R. Finn, J. G. Foley, M. W. Fowles, D. Gardner, D. H. Goldsmith, S. G. Gooch, Brenda Grant, W. B. Hanley, H. G. Harding, Gladys E. Hemes, J. W. Hill, H. B. Hilton, E. Holmes, E. J. M. Hopkins, [2]P. L. Jones, P. King, J. B. Laine, V. Leach, C. L. Levene, G. Lloyd, B. A. Lowe, Joan K. McCann, J. B. McFarland, N. McKie, Anne D. Micah, F. T. O'Brien, B. J. O'Dowd, J. B. Peters, Pearl Ramkallop, L. Ratoff, M. R. Rayman, A. Roberts, R. W. Royston, S. S. Rubenstein, M. J. Samuels, H. Savage, Eleanor K. Scott, T. F. Shelley, A. Speakman, A. Swithinbank, D. A. Thomas, R. S. Todd, V. Tonge, T. Trace, A. Turner, M. R. B. Wallice, W. P. Walsh, P. K. Wilson, G. H. Worsley, I. Worst, E. S. Wylie. *Passed in separate subjects*: I. K. Brown, P. A. Harrison, R. A. Yorke (surgery and obstetrics and gynaecology), B. J. Charlick, T. R. Evans, J. L. Mason, J. M. Nichols, Mary E. Shepherd (medicine and surgery), Patricia O. Grundy, T. R. T. Hughes, W. V. N. Pugh (medicine and obstetrics and gynaecology).

DIPLOMA IN PUBLIC HEALTH.—Ursula M. Anderson, G. T. Crook, Jeannette Diamond, A. W. Iljon, Joan Knowles, P. Lorigan, H. P. P. Morris, D. S. Parken, J. L. Paterson, Eira Thomas, Joyce K. Watkin.

DIPLOMA IN RADIOLOGY.—*Radiodiagnosis*: B. K. Bajaj, W. C. Heron, P. McCann. *Radiotherapy*: H J. J. Beyleveld.

[1]With second-class honours. [2]With distinction in surgery. [3]With distinction in obstetrics and gynaecology.

## UNIVERSITY OF SHEFFIELD

Drs. J. E. R. Scholtz and J. L. A. Dowse have been appointed full-time Demonstrators in Anatomy, and Mr. R. E. Peasegood part-time Clinical Teacher in Diseases of the Ear, Nose, and Throat.

Dr. E. W. Clarke, Lecturer in Physiology, and Dr. P. G. Walker, J. G. Graves Medical Research Fellow, have resigned their appointments.

Professor H. A. Krebs, F.R.S., Professor of Biochemistry, has resigned his appointment on his election to the Chair of Biochemistry in the University of Oxford.

Dr. G. R. Tudhope has been appointed full-time Lecturer in Therapeutics.

## UNIVERSITY OF BRISTOL

The following candidates have been approved at the examinations indicated:

FINAL M.B., CH.B.—[1 2 3 4]Mary E. Moore, [2 5 6]K. R. Gough, [2 5]D. B. Paintin, G. A. J. Ayliffe, [6]J. F. Baden-Daintree, V. Baker, C. A. Bickford, J. M. B. Burn, J. T. Bush, T. H. P. Chatfield, [4]J. R. Clamp, Mavis E. Coutts, G. G. Crabbe, Violet E. Dadds, R. N. Davies, G. N. Febry, D. W.

Fortune, Angela C. Fowler, D. B. Fowler, J. S. Hughes-Games, [3]J. L. James, F. E. S. Keiller, Jean D. Kelly, C. A. Milner, E. J. R. Morgan, D. G. Osmond, J. M. V. Packer, Ruth D. Penn, M. Roylance, R. K. M. Sanders, H. Savery, [6]R. Seymour-Shove, F. G. Spear, D. M. M. Thomson, D. H. Waldron, [6]M. R. Wills, G. C. B. Winter. *In Group I completing the examination:* J. A. Beel, M. J. Page. *In Group II only:* Pamela M. Atkinson.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part II:* A. E. P. Swinson.

[1]With first-class honours. [2]With second-class honours. [3]With distinction in child health. [4]With distinction in surgery. [5]With distinction in obstetrics. [6]With distinction in public health.

## ROYAL COLLEGE OF SURGEONS OF ENGLAND

Sir Harry Platt was elected President of the Royal College of Surgeons of England at a meeting of the Council held on July 8, in succession to Sir Cecil Wakeley, who has held office for the last five years. Professor Lambert Rogers and Mr. Julian Taylor were elected Vice-Presidents.

Mr. H. A. S. van den Brenk (Melbourne) was elected a Research Fellow in the H. N. Smith Research Unit.

Professors and Lecturers for the ensuing year were appointed as follows:

*Hunterian Professorships:* Mr. C. P. Wilson, one lecture on lateral cysts and fistulae of the neck of developmental origin; Mr. H. B. Stallard, one lecture on retinoblastoma treated by radon seeds, and radium risks; Mr. R. V. Cooke, one lecture on advanced carcinoma of the colon, with particular reference to the inflammatory factor; Mr. J. Foster, one lecture on evaluation of the current treatment of stricture of the valve of Krause; Mr. N. R. Barrett, one lecture on primary tumours of rib; Professor G. Causey, one lecture on the place of the vascular supply in fatigue and regeneration of peripheral nerve; Dr. W. T. Cooke, one lecture on nutritional and metabolic factors in the aetiology and treatment of regional ileitis; Mr. F. G. Kergin, one lecture; Mr. P. H. Newman, one lecture on spondylolisthesis, its cause and effect; Mr. H. R. S. Harley, one lecture on subphrenic abscess, with particular reference to the spread of infection; Mr. H. G. Hanley, one lecture on the surgery of male subfertility; Mr. R. Roaf, one lecture on the natural history of deformities as seen in India; Mr. W. J. Atkinson, one lecture on the early management of head injuries; Mr. A. C. Bingold, one lecture on benign fibrous tumours of single bones; Professor R. V. Bradlaw, one lecture; Mr. K. Harrison, one lecture on a study of ectopic mixed salivary tumours; Mr. J. McE. Potter, one lecture on angiomatous malformations of the brain: their nature and prognosis.

*Arris and Gale Lectures.*—Dr. B. D. Wyke, one lecture on the cortical control of movement: a contribution to the surgical physiology of seizure; Mr. A. G. Riddell, one lecture on ammonia intoxication in surgical patients; Dr. W. M. Keynes, one lecture on the anatomy and surgery of the supravesical fossa.

*Erasmus Wilson Demonstrators.*—Dr. B. E. Heard, one demonstration; Dr. G. D. Lumb, one demonstration; Dr. J. S. Young, one demonstration; Dr. L. M. Franks, one demonstration; Dr. L. W. Proger, one demonstration.

*Arnott Demonstrators.*—Professor G. Causey, one demonstration; Dr. F. Stansfield, two demonstrations; Professor R. J. Last, one demonstration; Dr. S. Engel, one demonstration; Dr. H. J. Hoffmann, one demonstration.

The Begley Prize was presented to M. Anthony Cowan (Sheffield).

Diplomas of Fellowship were granted to H. A. S. van den Brenk, H. N. Baylis, and G. E. Lynch.

## ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the College held on July 15, with Professor Walter Mercer, President, in the chair, the following candidates were admitted Fellows of the College, having passed the requisite examinations:

J. C. Allan, M. R. Ashbridge, M. A. Azam, A. A. Azie, I. J. Bryan, J. E. Church, J. Cook, S. DasGupta, V. G. Diwanker, B. J. van Rensburg Dreyer, D. Duncan, A. G. Foreman, A. Gol, D. S. Gordon, J. W. Jackson, M. J. Joubert, J. Katz, J. W. Kent, P. D. Livingstone, J. R. McCallum, H. B. Melzer, C. Miller, N. B. Mundy, G. S. Plaut, V. N. Purandare, A. S. Qazi, J. M. Robertson, H. M. Saba, K. Singh, K. Sivarajan, G. Stout, H. I. Tankel, O. L. Thomas, R. Vasudave, N. St. G. Wade, R. Sheng-Wu Wang, L. White.

## ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on July 20, with the President, Professor L. S. P. Davidson, in the chair, the following were elected Members of the College: F. F. Main, J. W. Crofton, A. G. Macgregor, C. M. Connolly, P. Crosby, J. R. McGregor, D. J. Attygalle, C. S. Ratnatunga, B. N. Krishnamurthy, A. K. M. Macrae, I. S. M. Fernando, V. Gorvy, K. L. Chopra, P. Harris, A. M. Khan, G. B. Landsman, A. G. Mezey, P. J. E. Lewis, B. L. C. Phillips, L. A. Dawson, H. E. Reef, M. Munro, D. F. Harris, Y. Rajasekhar, E. R. du Preez, J. C. Phemister, S. Parija, L. A. G. Davidson, D. I. Manson, A. J. Proust, M. L. Horn, R. Stepanian-Fard, Imtiaz-Ud D. Hasan, N. S. Ghani, M. D. W. Low, A. W. Reid, B. N. Sinha, F. M. W. Williams, P. M. Robb, G. F. M. Russell, E. Marley, V. E. Pollak, S. J. Powell, J. H. Allison, A. J. Keay.

## ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the College held on July 2 the President, Dr. Edward T. Freeman, admitted the following candidates to the Licence of Medicine and Midwifery:

G. L. N. Alderdice, Sheila M. Arnold, E. Barrett, E. J. Berstock, D. Bhana, F. Blain, A. C. Bradley, M. Brennan, B. P. de Brit, R. Brown, N. H. Coleman, A. C. Connolly, Vivian M. Cowin, T. B. Dobson, Helen M. Dunne, C. P. A. Dupont, Moira L. Franklin, L. R. Golicz, Louise M. Hamilton, J. E. Jolley, K. Jones, F. G. Kenny, J. L. Layng, Sybil E. K. Meharg, N. A. Moss, P. J. McCrann, A. I. MacKinnon, G. M Noel, L. M. Nurock, J. F. O'Connell, J. C. Murphy-O'Connor, E. H. O. B. Pratt, R. Rumian, Elsie L. M. Wallace, N. J. de Wet, Maria I. Znamirowska, and Iris Serruya (admitted on July 9).

## ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on July 24, with the President, Mr. Arthur A. Gemmell, in the chair, the following officers were re-elected: *President*, Mr. Arthur A. Gemmell; *Vice-Presidents*, Professor Gilbert I. Strachan, Mr. A. J. McNair; *Honorary Treasurer*, Mr. A. C. H. Bell; *Honorary Librarian*, Mr. A. J. McNair; *Honorary Treasurer, Australian Regional Council*, Mr. J. N. Chesterman; *Honorary Treasurer, Canadian Regional Council*, Mr. W. R. Foote; *Honorary Treasurer, New Zealand Regional Council*, Dr. J. E. Giesen. The following officers were elected: *Honorary Secretary*, Mr. I. MacG. Jackson; *Honorary Curator of the Museum*, Mr. R. A. Brews.

The following candidates were elected to the Membership:

G. J. Arendt, A. L. Baccarini, K. G. Ball, R. K. Banerjee, A. W. Banks, J. M. Barrett, Marjorie C. Bremner, A. E. R. Buckle, D. E. Burgess, J. D. Bury, Elizabeth B. Butler, K. W. Cochrane, J. V. M. Coppleson, J. Crossley, P. H. Crowe, G. T. M. Cummins, B. Danzig, K. Das Gupta, Sheila P. Davidson, D. J. Dooley, Mary M. Essex-Lopresti, R. A. W. Feakes, J. P. B. Fitzgerald, C. B. Gangamma, R. G. Gudex, Josephine M. R. Heber, Muriel S. Hill, D. Howell, M. H. Jamieson, P. E. Jeffery, E. W. Jeyaratnam, G. F. Jolly, D. Keith, B. L. G. Kneale, G. W. Korn, Marjorie A. C. Kuck, W. Lees, G. A. Lewis, G. D. R. Lilburne, W. G. McBride, E. V. Mackay, W. P. McLaughlin, M. C. Macnaughton, Joan Marshall, P. W. Mitchell, H. O'Hara, D. L. Phillips, H. M. Pretorius, W. L. G. Quinlivan, J. Roper, L. Rubin, B. M. Sandler, S. Sen Gupta, K. K. Sharma, Pamela M. Smith, A. E. M. Stevenson, D. Tacchi, J. G. A. Troup, J. Walsh, J. N. Ward, H. W. Wilson, L. H. Wilson.

## ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

At the annual meeting of the College held at Melbourne in May, the following office-bearers took office for 1954–6: *President*, Dr. C. G. McDonald; *Vice-Presidents*, Dr. Ralph Whishaw, Dr. A. D. S. Whyte, Dr. Ian J. Wood; *Censor-in-Chief*, Dr. T. M. Greenaway; *Honorary Treasurer*, Dr. W. P. MacCallum; *Honorary Secretary*, Dr. H. Maynard Rennie; *Past President*, Sir Alexander Murphy.

The following were elected to Fellowship:

P. Lesley Bidstrup, of the United Kingdom; C. R. Furner, S. J. M. Goulston, K. S. Harrison, Mary Heseltine, James Isbister, M. R. Joseph, V. J. McGovern, F. R. Magarey, S. Ralph Reader, and S. E. L. Stening, of New South Wales; D. G. Duffy, H. B. Kay, P. J. Parsons, W. McI. Rose, H. J. B. Stephens, and Marion Wanlis, of Victoria; H. N. Robson, J. M. Bonnin, and R. F. West, of South Australia; M. H. Aiken and C. G. Riley, of New Zealand.

The following, having satisfied the Board of Censors in Australia, were admitted to Membership by the President:

C. R. Boughton and J. C. Quoyle, of New South Wales; G. H. Neilson and J. J. Sullivan, of Queensland; S. G. Anderson, V. G. Bristow, K. G. Chatfield, A. Fisher, J. R. Kelly, W. R. Kingston, B. L. Marks, R. Motteram, and M. J. Robinson, of Victoria; A. K. Cohen, of South Australia; H. R. Elphick and O. B. Toller, of Western Australia.

The following, having satisfied the Board of Censors in New Zealand, were also admitted to Membership:

R. H. Caughey, H. K. Ibbertson, J. K. Laing, T. V. O'Donnell, and I. A. M. Prior, of New Zealand.

# Vital Statistics

### Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment was reported in June, 1954, was 121, compared with 75 (revised figure) in May and 119 (revised figure) in June, 1953.

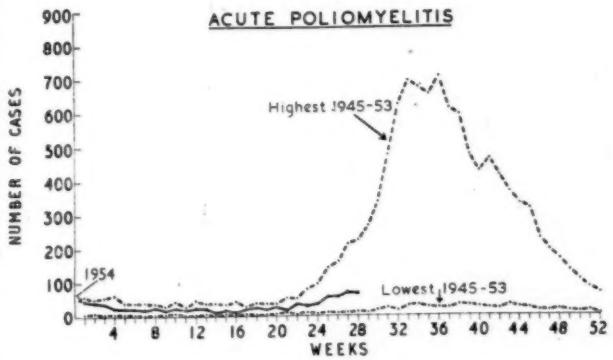
The number of cases of industrial diseases in the United Kingdom reported during June was as follows: lead-poisoning 4, other poisoning 3, anthrax 2, epitheliomatous ulceration 13, and chrome ulceration 16; total 38. There were no deaths.—*Ministry of Labour Gazette*, July, 1954.

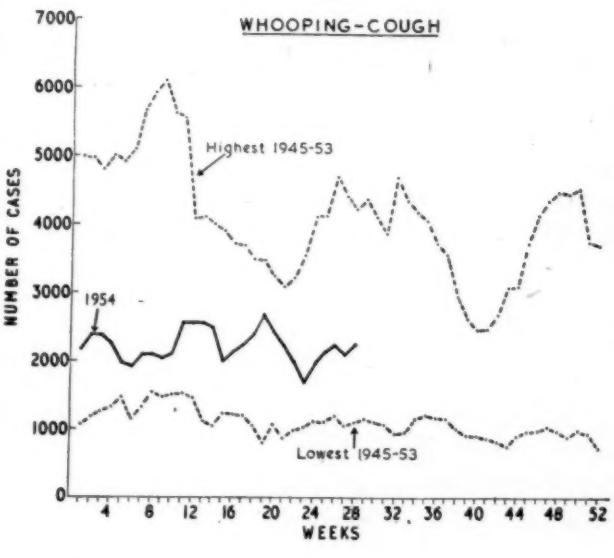
### Venereal Diseases

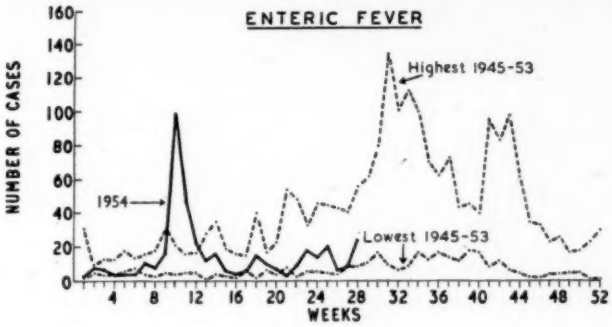
In England and Wales during the quarter ending March 31, 1954, 1,362 new cases of syphilis were reported as attending the clinics. Of these, 236 were classified as primary, secondary, or latent in the first year of infection. 17 cases of congenital syphilis in children aged under 1 year were reported, and 163 cases in persons over that age. New cases of gonorrhoea numbered 3,974, of chancroid 80, and of non-gonococcal urethritis (males only) 2,893.—*Monthly Bulletin of the Ministry of Health*, July, 1954.

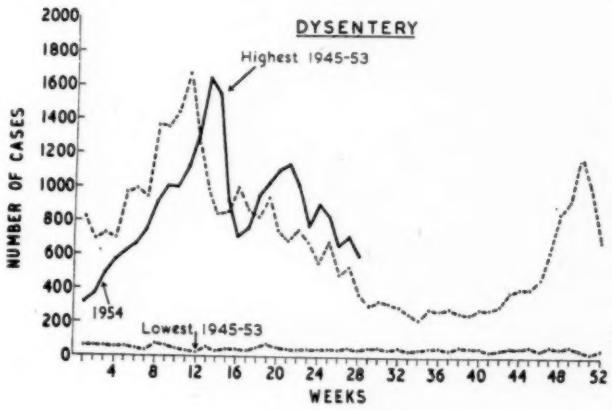
### Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.




### Infectious Diseases

The only variations of note in the trends of the notifications of infectious diseases in England and Wales during the week ending July 17 were increases of 383 for measles, from 2,690 to 3,073, and 150 for whooping-cough, from 2,085 to 2,235, and a decrease of 103 for dysentery, from 711 to 608.

The largest increases in the incidence of measles were 85 in Cheshire, from 254 to 339, 70 in London, from 121 to 191, 67 in Durham, from 271 to 338, 51 in Middlesex, from 66 to 117, and 51 in Gloucestershire, from 97 to 148. The largest variations in the trends of whooping-cough were a rise of 39 in Dorsetshire, from 14 to 53, and a fall of 43 in Derbyshire, from 77 to 34. 802 cases of scarlet fever were notified, 5 fewer than in the preceding week, and no large variations occurred in the local trends. 11 cases of diphtheria, 8 fewer than in the preceding week, were notified.

63 cases of acute poliomyelitis were notified, and these were 4 fewer for paralytic and 2 more for non-paralytic cases than in the preceding week. The largest returns were Durham 9 (Sunderland C.B. 3, Gateshead C.B. 2, Easington R.D. 2), London 6 (Woolwich 2), Staffordshire 6 (Walsall C.B. 3), Northumberland 6 (Newcastle-upon-Tyne C.B. 4, Castle Ward R.D. 2), Lancashire 5 (Liverpool C.B. 2).

5 of the 11 cases of typhoid fever were notified in Lancashire (Crosby M.B. 3). The chief centres of paratyphoid fever were Lancashire 4 (Whiston R.D. 3), and Surrey 4 (Surbiton M.B. 4).

The number of notifications of dysentery were the lowest since January. The largest returns were Yorkshire West Riding 99 (Sheffield C.B. 43, Leeds C.B. 10), Lancashire 94 (Manchester C.B. 25, Liverpool C.B. 17, Salford C.B. 11), London 76 (Fulham 18, Lewisham 15, Islington 10), Kent 64 (Penge U.D. 58), Leicestershire 31 (Leicester C.B. 25), Worcestershire 30 (Oldbury M.B. 27), and Durham 20.

### Week Ending July 24

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 785, whooping-cough 2,030, diphtheria 13, measles 2,965, acute pneumonia 254, acute poliomyelitis 91, dysentery 534, paratyphoid fever 9, and typhoid fever 3.

## INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 17** (No. 28) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire

| CASES in Countries and London | 1954 | | | | | 1953 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire |
| Diphtheria | 11 | 2 | 4 | 0 | 1 | 18 | 0 | 12 | 2 | 0 |
| Dysentery | 608 | 76 | 142 | 6 | 0 | 676 | 135 | 147 | 4 | 1 |
| Encephalitis, acute | 7 | 0 | 1 | 0 | | 2 | 0 | 0 | 0 | |
| Enteric fever: | | | | | | | | | | |
| Typhoid | 11 | 2 | 0 | 0 | 1 | 4 | 1 | 0 | 0 | 0 |
| Paratyphoid | 13 | 1 | 1 | 0 | 0 | 5 | 0 | 6(B) | 0 | 0 |
| Food-poisoning | 383 | 20 | | 3 | | 505 | | | 8 | |
| Infective enteritis or diarrhoea under 2 years | | | | 14 | 15 | | | | 22 | 18 |
| Measles* | 3,073 | 191 | 52 | 162 | 220 | 6,871 | 173 | 239 | 267 | 102 |
| Meningococcal infection | 37 | 1 | 9 | 2 | 0 | 43 | 4 | 17 | 0 | 2 |
| Ophthalmia neonatorum | 37 | 1 | 5 | 0 | | 31 | 2 | 11 | 0 | |
| Pneumonia† | 312 | 24 | 69 | 0 | 2 | 328 | 16 | 143 | 5 | |
| Poliomyelitis, acute: | | | | | | | | | | |
| Paralytic | 42 | 4 | } 9 | 2 | 2 | { 49 | 2 | } 4 | 6 | 2 |
| Non-paralytic | 21 | 2 | | | | { 11 | 2 | | | |
| Puerperal fever§ | 242 | 53 | 9 | 0 | 0 | 324 | 33 | 13 | 4 | 0 |
| Scarlet fever | 802 | 57 | 89 | 19 | 26 | 1,333 | 87 | 187 | 52 | 18 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory | 737 | 86 | 151 | 34 | | | | 144 | 29 | |
| Non-respiratory | 124 | 8 | 19 | 5 | | | | 36 | 6 | |
| Whooping-cough | 2,235 | 109 | 186 | 24 | 30 | 4,116 | 349 | 394 | 49 | 47 |

| DEATHS in Great Towns | 1954 | | | | | 1953 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire | Eng. & Wales | Lond. | Scot. | N. Ire. | Eire |
| Diphtheria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 |
| Dysentery | 0 | 0 | | 0 | | 3 | 0 | | | |
| Encephalitis, acute | | 0 | | | 0 | | 0 | | | 0 |
| Enteric fever | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | | |
| Infective enteritis or diarrhoea under 2 years | 6 | 6 | 0 | 0 | 1 | 8 | 0 | 4 | 0 | 1 |
| Influenza | 6 | 1 | 0 | 0 | 0 | 6 | 0 | 1 | 0 | 2 |
| Measles | | 0 | 0 | 0 | | | 0 | 0 | | 1 |
| Meningococcal infection | | 0 | 0 | | | | 1 | 0 | | |
| Pneumonia | 152 | 17 | 13 | 5 | 9 | 138 | 20 | 13 | 11 | 4 |
| Poliomyelitis, acute | 3 | 1 | | | 0 | 2 | 0 | | | 0 |
| Scarlet fever | | 0 | 0 | 0 | 0 | | 0 | 0 | | 0 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory | } 77 | { 8 | 8 | 2 | 2 | } 90 | { 11 | 12 | 1 | 10 |
| Non-respiratory | | 1 | 10 | 0 | 1 | | 1 | 3 | 0 | 2 |
| Whooping-cough | 3 | 1 | 1 | 0 | 0 | 2 | 0 | 2 | 0 | 0 |
| Deaths 0–1 year | 166 | 14 | 28 | 2 | 17 | 233 | 28 | 37 | 9 | 12 |
| Deaths (excluding stillbirths) | 4,446 | 626 | 480 | 90 | 150 | 4,649 | 657 | 508 | | 147 |
| LIVE BIRTHS | 7,615 | 1163 | 905 | 186 | 391 | 7,951 | 1232 | 879 | 235 | 368 |
| STILLBIRTHS | 203 | 31 | 23 | | | 211 | 19 | 28 | | |

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

# Medical News

**Royal College of Physicians of London.**—A quarterly comitia was held on July 29, with Sir RUSSELL BRAIN, President, in the chair. Sir JOHN CHARLES was appointed Harveian Orator and Dr. D. J. WILLIAMS Bradshaw Lecturer, both for 1955. The following Lecturers were also appointed for 1955: *Lumleian*, Dr. A. M. COOKE; *Goulstonian*, Dr. G. M. BULL; *Oliver-Sharpey*, Professor W. M. ARNOTT; *Charles West*, Dr. W. P. H. SHELDON; *F. E. Williams*, Lord AMULREE; and *Ernestine Henry*, Dr. K. M. A. PERRY. The following were appointed lecturers for 1956: *Croonian*, Dr. A. H. DOUTHWAITE; *Fitz-Patrick*, Dr. TERENCE EAST; and *Watson Smith*, Dr. R. T. BRAIN. The Moxon Medal for 1954 was awarded to Dr. J. L. GAMBLE, of Boston, for his contributions to the knowledge of the significance of disturbances of electrolyte metabolism in clinical medicine. The Weber–Parkes prize for 1954 was awarded to Mr. H. MORRISTON DAVIES for his pioneer contributions to the surgical treatment of pulmonary tuberculosis. The Murchison scholarship was awarded to Dr. E. D. R. CAMPBELL.

**Chair of Surgery at St. Thomas's.**—Mr. J. B. KINMONTH, reader in surgery at St. Bartholomew's Hospital, has been appointed to the London University chair of surgery tenable at St. Thomas's Hospital Medical School. Mr. Kinmonth qualified at St. Thomas's in 1938, and after holding resident appointments there was awarded a London University travelling fellowship in surgery. He also held a research fellowship in surgery at Harvard. In 1951 he was Arris and Gale lecturer of the Royal College of Surgeons, and in 1954 a Hunterian professor. Mr. Kinmonth's main contributions have been in the field of vascular surgery.

**Royal College of Surgeons.**—At a meeting of the council on July 29, with Sir HARRY PLATT, P.R.C.S., in the chair, Professor V. F. LAMBERT was admitted to the Court of Examiners. A Moynihan lectureship was awarded to Dr. OSWALDO P. CAMPOS, of Rio de Janeiro. The Hallett prize was awarded jointly to Mr. G. S. M. BOTHA (Capetown) and Mr. J. D. N. YELLAND (Queensland), and the Handcock prize to Mr. M. J. A. BRITTEN (Liverpool). It was reported that the Medical Research Council had agreed to make a grant to finance the research in ophthalmological genetics to be carried out in the Ophthalmological Research Department of the College.

**Nichols Fellowship.**—The council of the Royal Society of Medicine, on the recommendation of the Section of Obstetrics and Gynaecology, has awarded the Nichols Fellowship to Dr. NORMAN MORRIS for research on pre-eclampsia and essential hypertension in pregnancy.

**Faculty of Ophthalmologists.**—At the council meeting held on July 23 the following were elected officers for 1954–5: *president*, Mr. J. H. DOGGART; *vice-presidents*, Dr. JOHN MARSHALL and Mr. T. KEITH LYLE; *hon. treasurer*, Mr. A. MCKIE REID; and *hon. secretary*, Mr. E. F. KING.

**"Family Doctor."**—The August issue opens with an article by JOYCE CARY, "A Child's Religion." Medical subjects discussed include vaccination (Dr. T. ANDERSON), the heredity of the special senses (ROGER PILKINGTON), anaemia, and the abilities of babies (Sir CYRIL BURT). The career profile is "Operating Theatre Technicians." Copies are obtainable at 1s. 6d. from any bookseller.

**Ruthin Castle Clinic,** the well-known private clinic in North Wales, has recently been taken over by an English company. It is planned to modernize the clinic and increase the amenities for patients. Dr. S. W. PATTERSON remains as the senior physician.

**"The British Medical Bulletin,"** published by the British Council, now appears three times a year. The term "Bulletin" may be a bit misleading, as successive numbers

of it are in fact valuable symposia of various aspects of scientific medicine, the articles in the symposia being contributed by recognized British authorities on the subjects dealt with. The first number of the *Bulletin* for this year (price 15s.) is on "Reactions to Injury." The 16 contributions on this theme are preceded by an introduction by Sir EDWARD MELLANBY. The second number of the *Bulletin* (price 15s.), now available, is on tuberculosis, the 15 articles on this being preceded by an introduction by Dr. P. D'ARCY HART. The third *Bulletin*, to be published later this year, will be on chromatography (price 15s.). Separate issues or the complete volume (price £2) may be obtained from booksellers or from the Medical Department, The British Council, 65, Davies Street, London, W.1.

**Methylpentynol.**—The council of the Pharmaceutical Society of Great Britain states that it views with increasing anxiety the notices given to methylpentynol and its applications in various newspapers. It has advised its members to supply the drug only on a medical or dental prescription.

**Dr. G. W. A. Dick,** of the Medical Research Council, has been appointed to the chair of bacteriology at the Queen's University.

**Sir Cecil Wakeley** has been elected president of the Chartered Society of Physiotherapy in succession to Sir Harry Platt, P.R.C.S.

**Dr. Alexander Mair,** senior lecturer in social medicine, St. Andrews University, has been appointed to the James Mackenzie chair of public health and social medicine.

**Students' Conference.**—On July 28 at Scottish House, Edinburgh, the chairman's subcommittee on behalf of the Scottish Committee of the B.M.A. entertained at a sherry party delegates attending the Students' International Clinical Conference organized by the British Medical Students' Association. The guests were received by Dr. and Mrs. J. G. M. HAMILTON. In a speech of welcome Dr. Hamilton emphasized that medicine was a calling which knew no frontiers. When doctors met each other abroad they did not meet as foreigners, but as colleagues. Professor T. J. MACKIE, dean of Edinburgh University Medical School, associated himself with Dr. Hamilton's welcome, and endorsed what he had said about the value of students from all countries meeting together in this way.

## COMING EVENTS

**"The Numbers of Man and Animals."**—Symposium arranged by Institute of Biology at the Royal Geographical Society, London, on September 24 and 25. Speakers include Dr. A. S. PARKES, F.R.S., Professor A. L. BANKS, Dr. J. HAMMOND, F.R.S., Dr. F. FRASER DARLING, Professor L. S. PENROSE, F.R.S., and Lord BOYD-ORR, F.R.S. Further information from General Secretary, Institute of Biology, Tavistock House South, Tavistock Square, London, W.C.1.

**Third Conference of British Occupational Hygiene Society.**—At the London School of Hygiene and Tropical Medicine on November 1. Discussion on radiation hazards in industry. Further information from Mr. P. C. G. Isaac, Public Health Engineering Laboratory, King's College, Newcastle-upon-Tyne.

## BIRTHS, MARRIAGES, AND DEATHS

### BIRTHS

**Alms.**—On July 16, 1954, in Mauritius, to Beryl, wife of Michael Alms, F.R.C.S., a sister for Harriet and Richard—Charlotte Kimi.

**Way.**—On July 26, 1954, at Mill Road Maternity Hospital, Liverpool, to Hedi (formerly Papigay), L.R.C.P.&S.Ed., wife of Dr. Gilbert Way, a son.

### DEATHS

**Cordiner.**—On July 6, 1954, at Hull, East Yorks, Hew Beaton Cordiner, M.B., Ch.B., aged 55.

**Green.**—On July 25, 1954, at Sheffield Royal Infirmary, Douglas Green, M.B., F.R.C.S., of 2, Camping Lane, Sheffield.

**Shirlaw.**—On July 26, 1954, at his home, The Hall Green, Upholland, Lancs, John Thomson Shirlaw, M.D.

# Any Questions?

*Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.*

### Treatment of Tics

**Q.**—*What place has psychotherapy (including hypnosis) in the treatment of a severe and long-established habit spasm in an adult? He also suffers from an anxiety state.*

**A.**—A habit-spasm or motor tic is very difficult to relieve, except by section of the appropriate motor nerves with resulting paralysis. Either the pattern is ingrained in the nervous pathways or the tic itself is an expression of central, often extrapyramidal, nervous disease. Anxiety states are commonly found in patients with habit spasm, who are said often to be sensitive and intelligent people. In some cases an underlying nervous defect both causes the tic and predisposes to anxiety, which, in its turn, makes the tic worse.

The tic often varies in severity with the patient's mental state, and treatment of the anxiety either by psychotherapy or symptomatically with sedatives may lessen the movements. When the patient is of an anxious constitution and the anxiety state is chronic, psychotherapy may not be practicable. On the other hand, movements of this kind are well known to respond temporarily to suggestion under deep hypnosis, if this can be induced. The duration of the improvement varies from a few minutes after the hypnosis has been terminated to a useful remission. The results described have not, however, been followed up for very long. Suggestion never works so well on the second occasion. One should be circumspect about removing a non-disabling symptom to which the patient has been accustomed for a long time, and the reasons why he seeks treatment at this particular moment should be sought.

### Post-gastrectomy Syndromes

**Q.**—*What are the common post-gastrectomy syndromes? What is their explanation, and how should they be treated?*

**A.**—There are two post-gastrectomy syndromes which may appear as soon as the patient starts to take full meals after operation. They are classified according to the time of their appearance after food.

The early syndrome appears about 20 minutes after the ingestion of food, and colloquially is called "dumping," because of the radiographic observation that after gastrectomy a barium meal falls rapidly into the coils of jejunum lying in the pelvis. This was mistakenly considered to be the cause of the symptoms. The early syndrome occurs in about 12% of patients who have had the Polya operation, it lasts for about 30 minutes, and is cured by lying down. The chief symptoms are sweating, palpitations, tachycardia, epigastric fullness, and distress. Its severity depends chiefly on the bulk of the meal ingested, and may be worse after certain types of food, such as sugar or milk. It may be associated with periodic vomiting of small amounts of bile, coming on two or three times a week. The condition usually gradually subsides and disappears about a year after gastrectomy. In about 3% of cases, however, it persists indefinitely and may completely disable the patient. Its exact aetiology is not known. It does not occur to any extent after the Billroth I operation. It is undoubtedly associated with distension and the increased weight of the afferent loop, and is prevented in most cases by adequate support of the lesser curve of the stomach and the afferent loop. Probably the osmotic disturbance produced by a large amount of hypertonic glucose deposited suddenly in the jejunum is also a factor. Considerable experimentation is still going on in order to determine the exact cause.

Mild cases need only encouragement and reassurance. In more severe cases it is wise to advise patients to take their

meals dry and to avoid hypertonic drinks of glucose or milk. Sometimes sodium bicarbonate before a meal will help, and in other cases hexamethonium in small doses is helpful. Meat at the beginning of the meal may ward off the symptoms, or sometimes lying down immediately after the main meal of the day may be sufficient. It is only in the most severe and crippling cases that further operation is necessary. If this becomes imperative, it is best to convert the Polya to a Billroth I anastomosis, or else to support the lesser curve of the stomach and the afferent loop very firmly to the remains of the gastro-hepatic omentum. In some cases patients who have had indigestion for years will say that a bit of dizziness after meals, and lassitude, with occasional biliary vomiting, is a small price to pay for the complete freedom from pain they have after operation.

The late syndrome comes on about two and a half hours after a meal, and is entirely due to a low blood sugar. The common symptoms are tremor of the limbs, giddiness, and profuse perspiration. For some as yet unexplained reason the blood sugar is low at this stage of digestion and the symptoms respond rapidly to some sugar by mouth or to two-hourly feeding. As soon as the blood sugar rises, the symptoms disappear. It can easily be distinguished from the early syndrome by its time of onset and its response to more food. No special treatment is necessary in this condition, as it always disappears after two or three years. It must be emphasized that these post-gastrectomy syndromes are not common, and usually do not cause any serious inconvenience.

### Antituberculosis Drugs and the Heart

**Q.**—*Is there any evidence to suggest that anti-tuberculosis drugs such as streptomycin, P.A.S., or isoniazid are harmful to the heart in any way? I have had a patient with a history of previous coronary infarction who developed auricular fibrillation after streptomycin, which reverted to normal rhythm on digoxin, but later when given P.A.S., streptomycin, and isoniazid again developed a cardiac arrhythmia and died suddenly.*

**A.**—The only drug used which might have had an effect on the heart is P.A.S. (*para*-aminosalicylic acid). Potassium deficiency, with weakness and cardiac irregularity, has been described in patients treated with P.A.S.,[1 2] though there is evidence that the liquorice sometimes used as a flavouring agent may be the important factor.[3] Streptomycin and P.A.S. are more apt to delay blood clotting than induce thrombosis, though the concentrations necessary for this effect are unlikely to be reached with the usual clinical doses.[4]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1 Cayley, F. E. de W. (1950). *Lancet*, **1**, 447.
2 Heard, K. H., *et al.* (1950). *Med. J. Aust.*, **2**, 606.
3 Strong, J. A. (1951). *British Medical Journal*, **2**, 998.
4 Walther, G., and Winter, K-A. (1952). *Klin. Wschr.*, **30**, 25.


### Iron in the Water Supply

**Q.**—*Chemical analysis of a sample of water from a borehole shows that iron is present to the extent of 0.25 part per 100,000. As the permissible limit for this metal is usually given as 0.05, what ill effects would result from the continued use of this water for human consumption? Should this water be condemned despite the fact that the chemical analysis is satisfactory in all other respects?*

**A.**—Quite small concentrations of iron in water preclude its use by reason of an unpleasant inky taste and of undesirable staining effects when the water is used for laundering and other purposes. In addition, iron-bearing waters are prone to the development of crenothrix and other growths in the distribution system. The concentrations of iron which condemn a water on such grounds are, moreover, but a very small fraction of those at which its wholesomeness would be impaired. The limit is thus one set by suitability and not by considerations of health.

It may be taken in general that a supply should not contain more than 0.03 part per 100,000 of iron. If this figure is appreciably exceeded, even though the water be clear at its source, discoloration or even deposition of a reddish deposit of iron oxide may occur subsequently. Fortunately the removal of iron from water is not often difficult and a process involving aeration followed by filtration or sedimentation is usually sufficient to remove all but the merest trace. If, as the inquirer states, the supply is satisfactory in all other respects, an approach might be made to the makers of equipment for water treatment who would suggest measures appropriate to the supply in question.

### Local Analgesics for Scalds

**Q.**—*Is there any local analgesic which is effective when applied to the unbroken skin? I have in mind the relief of pain due to burns and scalds.*

**A.**—I do not know of any such. There are various creams and ointments on the market which are reputedly analgesic, but a few months ago I and my staff tried them all out; we rubbed ourselves diligently but produced no anaesthesia of the skin.

## NOTES AND COMMENTS

**Post-vaccinial Encephalitis.**—In a leading article on encephalitis in childhood (June 5, p. 1312) it was stated that post-vaccinial encephalitis "is almost never seen when primary vaccination is undertaken in the first year of life." We understand from the General Register Office that between the years 1936 and 1952 there were 26 deaths from post-vaccinial encephalitis in children under 1 year of age in England and Wales. These represent about two-fifths of the total mortality from post-vaccinial encephalitis during this period.

### Corrections

In our account (July 24, p. 229) of the meeting of the Sections of Occupational Health and Ophthalmology during the Annual Meeting at Glasgow, Mr. E. Gordon Mackie is reported to have said that "those who became partially sighted did so usually as a result of sudden visual loss. . . ." What Mr. Mackie actually said was: "The partially sighted children are already cared for under the school ophthalmic service and progress naturally through education to suitable employment. Our special problem in this discussion is the adult who becomes partially sighted by sudden visual loss."

On p. 312 of our issue of July 31 Professor John Fulton was wrongly described as of Harvard. He is, of course, Sterling Professor of the History of Medicine at Yale.

Professor DOUGLAS KERR writes: "You report me as saying at the meeting of the Section of Forensic Medicine at Glasgow (July 24, p. 226) that alcohol had been exaggerated as a cause of road accidents and only five per thousand could be attributed to that cause. This suggests that I think alcohol is only a minor cause of road accidents, which is just the reverse of what I actually said. These remarks apply to drivers certified as being drunk, and I went on to state that a much larger and much more dangerous category of drivers was the driver who had been drinking to excess but who was not drunk. The whole point of this part of my address was to emphasize that people only thought about the drunken driver, whereas a much more dangerous and more numerous class was the driver who was not quite drunk, and I made a plea for fresh legislation to bring these dangerous drivers within the law."

It was Sir Francis Walshe, not Sir William Gilliatt, who conferred the honorary Fellowships of the Royal Society of Medicine reported in the *Journal* of July 31, p. 312.

The second paragraph under the heading "Royal College of Physicians of Edinburgh" in the *Journal* of July 31 (p. 310) should have been headed "Royal College of Surgeons of Edinburgh." It reported a meeting of that College held on May 26.


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